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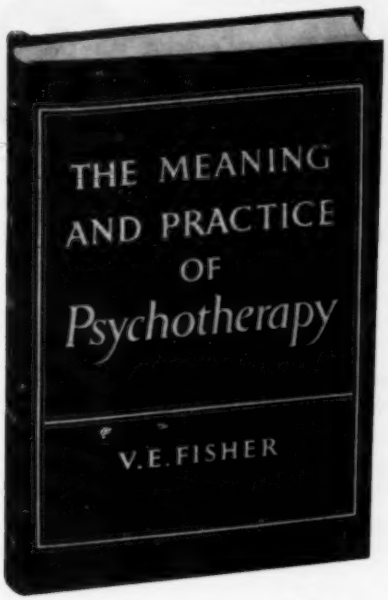

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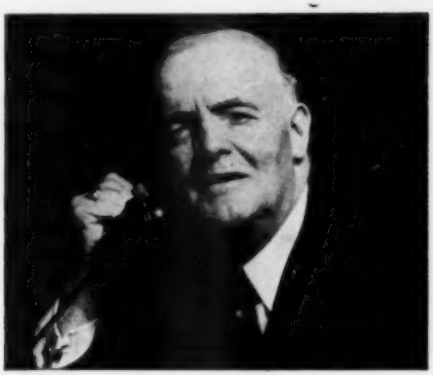

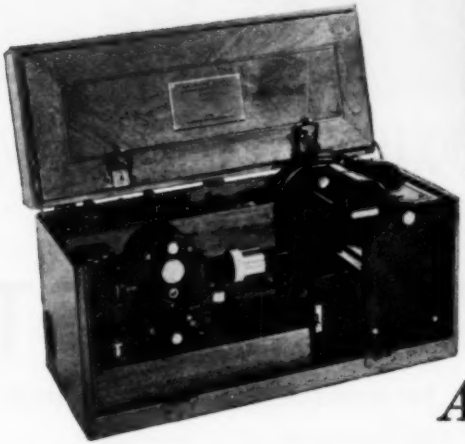

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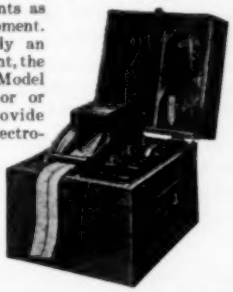

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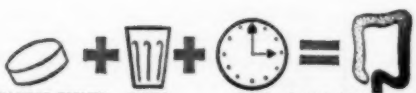

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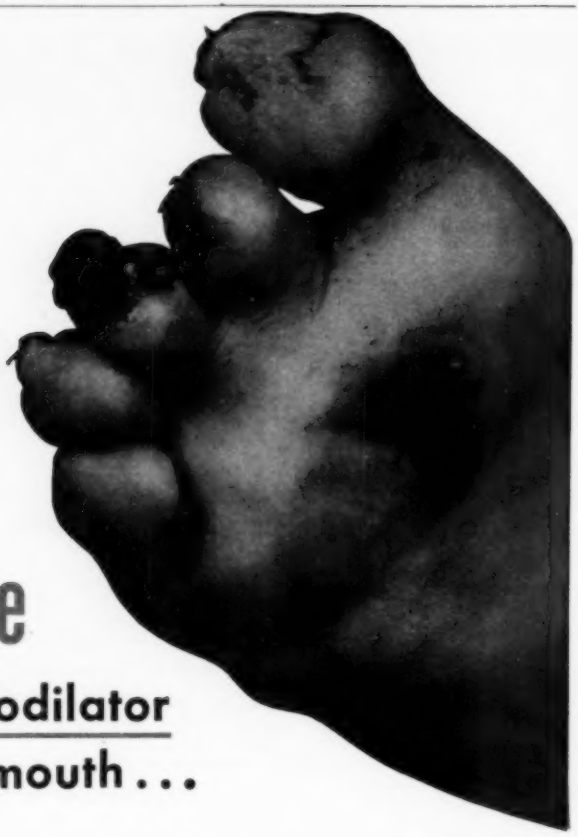

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1. Rogers, Max P.: J.A.M.A., May 21, 1949
2. Wyatt, Bernard L.: Ann. West. Med. & Surg., Aug. 1949
3. Grimson, Marzoni, Reardon & Hendrix: Ann. Surg., 127:5, May 1948

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"Not often do either globin insulin or a 2:1 mixture require supplementary use of regular insulin. Fully 80% of all severe diabetics can be balanced satisfactorily with one of them."[2]

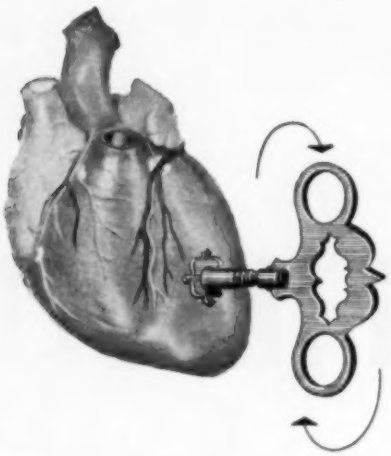
1. *Reeb, B. B., Rohr, J. R., and Colwell, A. R.: Proc. House Staff Dept. Med., Wesley Memorial Hospital, Chicago, Ill. Feb. 6, 1948.*

2. *Rohr, J. H., and Colwell, A. R., Proc. Amer. Diabetes Assn. 8:77, 1948.*

COMPLETE CLINICAL INFORMATION WILL BE SENT ON REQUEST

'Wellcome' brand Globin Insulin with Zinc, 'B. W. & Co.'®
is supplied in vials of 10 cc., U-40 and U-80

BURROUGHS WELLCOME & CO., (U.S.A.) INC., TUCKAHOE 7, NEW YORK



if only it were this SIMPLE

Until there are mechanical means for winding-up the failing heart . . . consider this: Nativelle isolated Digitaline to minimize the disadvantages of whole leaf. He replaced variable results with the *predictable effects* of dosage by weight. Digitaline Nativelle digitalizes in a few hours and *maintains the maximum efficiency obtainable. This maintenance is positive!* Complete absorption and a uniform rate of dissipation provide full digitalis effect between doses. Elimination of crude substances virtually eliminates side effects.

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Chief active principle of digitalis purpurea (digitoxin)

Ease of Administration

RAPID DIGITALIZATION: 1.2 mg. in equally divided doses of 0.6 mg. at three-hour intervals.

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CHANGE-OVER: Prescribe 0.1 or 0.2 mg. of Digitaline Nativelle to replace maintenance doses of 0.1 gm. or 0.2 gm. of whole leaf.

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prolonged distress until a specific allergen is discovered and—if possible—eliminated. Rapid, sustained relief can usually be obtained with **BENADRYL**, pioneer antihistaminic.

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BENADRYL® *pioneer antihistaminic*

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the probability of thrombi...

Both morbidity and mortality from postoperative venous thrombosis and embolism, frequent sequelae to surgery, have been dramatically reduced by early institution of anticoagulant therapy. Studies of anticoagulants by Upjohn research workers have led to the development of many Heparin Sodium preparations, including long-acting Depo*-Heparin Sodium, with or without vasoconstrictors. Heparin Sodium preparations provide promptly effective and readily controllable anticoagulant therapy.

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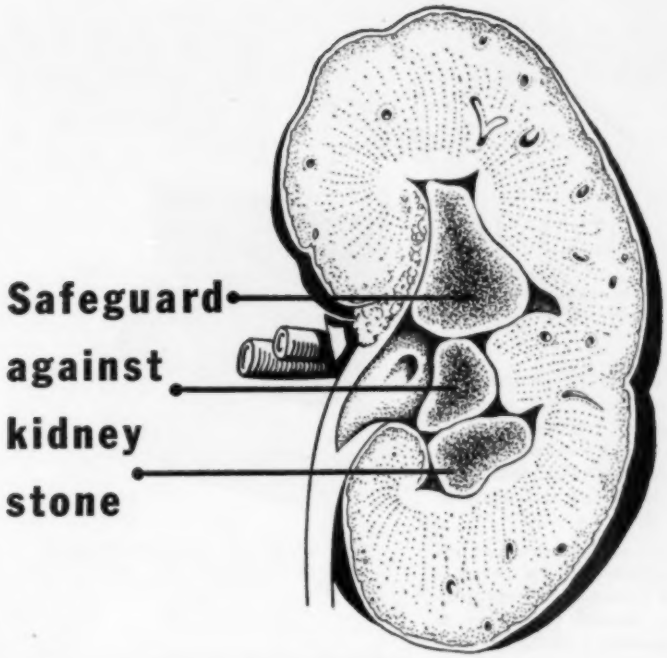

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Specifically for management and prophylaxis of recurrent renal stone

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long- lasting relief

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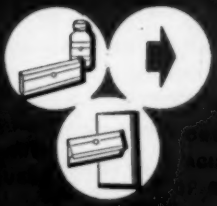

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When pain, heartburn, belching, nausea, or unstable colon are due to gastrointestinal spasm, Mesopin provides an effective means for prompt relief. Its selective antispasmodic action on the digestive tract controls spasticity without the undesirable side effects of atropine or belladonna. Thus, symptomatic relief of many common disturbances of the stomach or intestines can be achieved with discrimination and safety. Mesopin is indicated for the relief of gastrointestinal spasticity, such as pylorospasm, cardiospasm, spastic colon, and biliary spasm.

MESOPIN (brand of homatropine methyl bromide)

SELECTIVE GASTROINTESTINAL ANTISPASMODIC

SUPPLY: Elixir in 16 ounce bottles; tablets in bottles of 100.
MESOPIN (homatropine methyl bromide)—2.5 mg. per teaspoonful of elixir or per tablet. Also supplied: MESOPIN-PB*—2.5 mg. Mesopin and 15 mg. (1/4 gr.) phenobarbital per teaspoonful of elixir or per tablet.

Detailed literature and samples on request.

Endo®

*PB abbreviated designation for phenobarbital.

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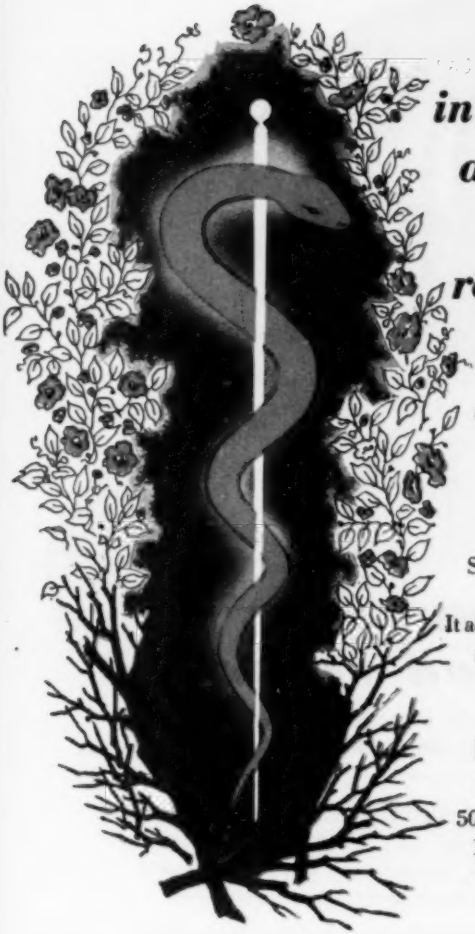

in active rheumatoid arthritis, the "best agent . . . that is readily available."[1]

Many therapeutic agents have been advocated for the treatment of active rheumatoid arthritis, with varying degrees of success. Among those now generally available, gold is "the only single form of therapy which will give significant improvement."[2]

SOLGANAL® for intramuscular injection is practical and readily available therapy. It acts decisively, inducing "almost complete remission of symptoms" in fifty per cent of patients and definite improvement in twenty per cent more.[3]

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Suspension SOLGANAL in Oil 10, 25 and 50 mg. in 1.5 cc. ampuls; boxes of 1 and 10 ampuls. Multiple dose vials of 10 cc. containing 10, 50 and 100 mg. per cc.; boxes of 1 vial.

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(aurothioglucose)

BIBLIOGRAPHY (1) Holbrook, W. P.: New York Med. (no. 7) 4:17, 1948. (2) Ragan, C., and Boots, R. H.: New York Med. (no. 7) 2:21, 1946. (3) Rawls, W. B.; Grunkin, B. J.; Ressa, A. A.; Dworzan, H. J.; and Schreiber, D.: Am. J. M. Sc. 207:528, 1944.

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THE "*Proxy-Emulsifier*" FOR
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Whatever the causes of steatorrhea – be it sprue or following subtotal gastrectomy – high fecal fat excretion can rapidly lead to a cachectic, fat-starved patient.

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Monitan is the first palatable preparation offering Sorbitan Monooleate Polyoxyethylene Derivatives in liquid form. Each teaspoonful (5 cc.) of Monitan provides 1.5 Grams of this substance (P.S.M.). It is orange flavored and easily administered to infants, children and the aged. Literature available.

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In 12 oz. bottles. Dosage: adults 1 to 2 teaspoonfuls three times daily with meals.

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". . . the diuretic drugs not only promote fluid loss but in many instances also effectively relieve dyspnea . . . not only may the load on the heart be decreased but there may also occur an increase in the organ's ability to carry its load . . . With good average response the patient perhaps voids about 2000 cc. of urine daily, but in exceptional instances the amount rises to as high as 8000 cc."[1]

"Not only are the diuretics of immense value in cases of left ventricular failure . . . but where edema is marked, as it is most likely to be in failures occurring in individuals with chronic nonvalvular disease with or without hypertension and arrhythmia, their employment is often productive of an excellent response. In [edematous patients with] active rheumatic carditis (rheumatic fever)the use of these drugs may be life-saving."[2]

Salyrgan-Theophylline is effective by muscle, vein or mouth.

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1. Beckman, H.: Treatment in General Practice. Philadelphia, Saunders, 5th ed., 1946, 784-785.
2. Beckman, H.: Treatment in General Practice. Philadelphia, Saunders, 6th ed., 1948, 744.

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3 Useful Cardiac Drugs

❶ Thesodate — Brewer IN ANGINA PECTORIS

(Theobromine Sodium Acetate 7½ gr. enteric coated)

Thesodate has been proven effective in increasing the capacity for work in individuals suffering from coronary artery disease. One Thesodate tablet four times a day (after meals and at bedtime) helps to maintain improved heart action and increased coronary artery circulation.

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(Potassium Iodide one gram or half gram enteric coated)

Enkide is useful as an adjuvant in tertiary syphilis and wherever potassium iodide therapy is indicated. Enkide insures accuracy of dosage, absence of gastric irritation and convenience of administration. Patients are more apt to follow prescription directions because of these advantages.

❸ Amchlor — Brewer IN CARDIAC EDEMA

(Ammonium Chloride one gram enteric coated)

Amchlor cuts in half the number of tablets each patient takes when large amounts of ammonium chloride are prescribed. This convenience to the patient helps to insure full and complete use of the entire amount prescribed. Amchlor is useful in cardiac edema, hypertension, dysmenorrhea, Meniere's Syndrome, etc.

Samples and Literature Available Upon Request.

Brewer EST. 1852

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Among the conditions in which Cortone has produced striking clinical improvement are:

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CORTONE is available for use in hospitals having facilities for required laboratory studies, and also for use in nonhospitalized cases following initial therapy in such hospitals. These hospitals can supply physicians' requirements for Cortone.

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THE usual pattern of response to CORTONE begins with diminution in subjective stiffness, commonly within 24 to 48 hours, but sometimes within 6 hours after the initial dose. In many cases this symptom is significantly or completely relieved within a few days. Next, articular tenderness and pain on motion decrease. Finally, swellings of the joints diminish, sometimes fairly rapidly and completely, but occasionally more slowly and incompletely.

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Appetite usually improves rapidly, and many patients have described a loss of the feeling of malaise associated with the disease and have experienced a sense of well-being, occasionally within several hours after initial administration of the drug.

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ACETATE
(CORTISONE Acetate Merck)
(11-Dehydro-17-hydroxycorticosterone-21-Acetate)

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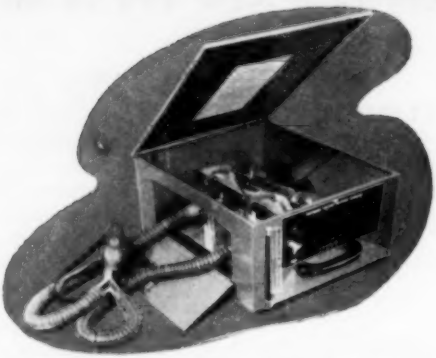
A PRODUCT OF O.E.M. CORPORATION

The ONLY Continuous Positive Pressure Breathing Machine



A VALUABLE THERAPEUTIC ADJUNCT TO THE TREATMENT OF

- ***acute pulmonary edema***
- ***severe asthma***
- ***obstructive lesions of larynx or trachea including obstructive dyspneas***

In these conditions the action of oxygen or helium-oxygen mixtures is two fold. The physical effort of the subject is decreased consequently decreasing dyspnea and counteracting internal hydrostatic pressure.

For Use With Both Oxygen And Helium-Oxygen Mixtures

References:

1. *Pressure-Breathing with oxygen and Helium-oxygen in Pulmonary Edema and Obstructive Dyspnea, Hylan A. Bickerman, M.D., Bulletin of the New York Academy of Medicine, June 1950, Vol. 26, No. 6.*

2. *Physiological Therapy in Respiratory Diseases, Alvan L. Barach, M.D., Chapter 7, pages 120-121, 131, 156; Chapter 8, pages 162-164; Chapter 25, pages 359-361.*

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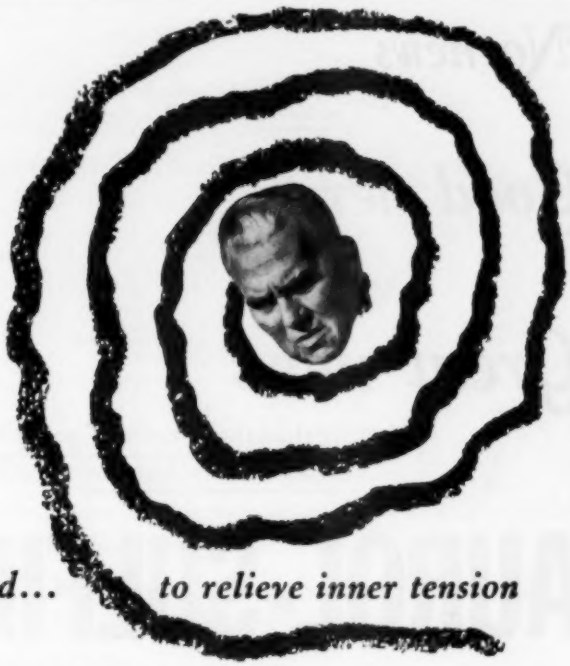

to ameliorate mood... to relieve inner tension

'DEXAMYL'—a balanced combination of 'Dexedrine'* and 'Amytal'†
—provides the beneficial effects of both its two components:

The 'Dexedrine', because of its "smooth" and profound antidepressant action, restores mental alertness and optimism and dispels psychogenic fatigue.

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Combined in DEXAMYL, the two components work together synergistically to control troublesome symptoms of mental and emotional distress.

Widely useful in everyday practice, 'Dexamyl' tablets are available in bottles of 50. Each tablet contains 'Dexedrine' Sulfate (dextro-amphetamine sulfate, S.K.F.) 5 mg. and 'Amytal' (Amobarbital, Lilly) ½ grain (32 mg.).

Smith, Kline & French Laboratories, Philadelphia

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is that *gold therapy* is now generally recognized as the *best available treatment* in several forms of *arthritis.*

Good news

is the *complete reversibility* in nearly all cases, *of rheumatoid arthritis* in its early stages.

Great news

is that the *benefits of gold therapy in arthritis* are now *available without risk* of 30–40% of toxic reactions.

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in reducing the toxicity of the gold salts to the point of practical elimination—while retaining the therapeutic value of the gold salts in arthritis—*extends the blessings of gold therapy from the hospital to the daily practice of every internist.*

Aurol-Sulfide 2% (intramuscular, intravenous) contains *20 mg. gold sulfide or 17.2 mg. metallic gold in each cc.* 15 cc; 30 cc; 60 cc vials.

Aurol-Sulfide 1% is for oral use where indicated.

How Aurol-Sulfide was made possible, is the secret of

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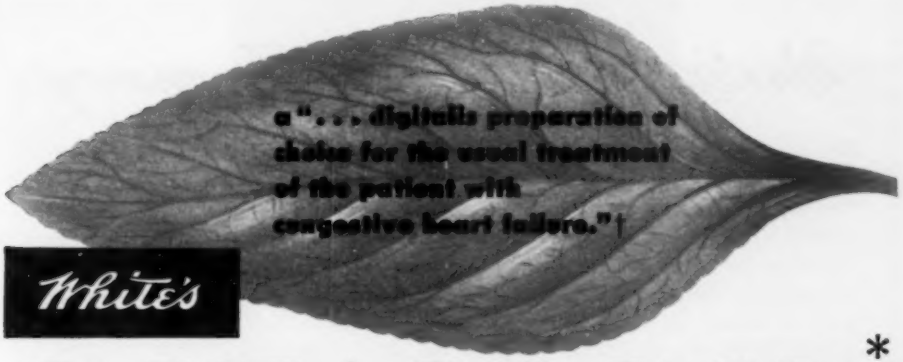


GITALIGIN*

AMORPHOUS GITALIN—PURIFIED CARDIOACTIVE GLYCOSIDAL CONSTITUENT OF DIGITALIS PURPUREA

(ji-tal-i-jin)

In the above carefully chosen words, Batterman, DeGraff and coworkers† sum up their conclusions following a four-year controlled clinical study in approximately 230 cases.

PROVED CLINICAL ADVANTAGES:

1. LARGE MARGIN OF SAFETY—Gitaligin offers a high degree of safety in initial digitalization and in establishing maintenance dose.

2. MODERATE RATE OF ELIMINATION—not as cumulative as digitoxin or digitalis leaf.

3. SHORTER LATENT PERIOD—than digitoxin or digitalis leaf.

4. UNIFORM CLINICAL POTENCY—unlike digitalis leaf.

5. PREDICTABILITY OF DOSAGE—dose expressed in weight, not units.

Pharmacological evidence indicates that Gitaligin is practically completely absorbed from the bowel.

WHITE LABORATORIES, INC., Pharmaceutical Manufacturers, Newark 7, N. J.

†Batterman, A. C., and coworkers: Studies with Gitalin (amorphous) for Treatment of Patients with Congestive Heart Failure, Federation Proceedings 9:256-257 (March) 1950.

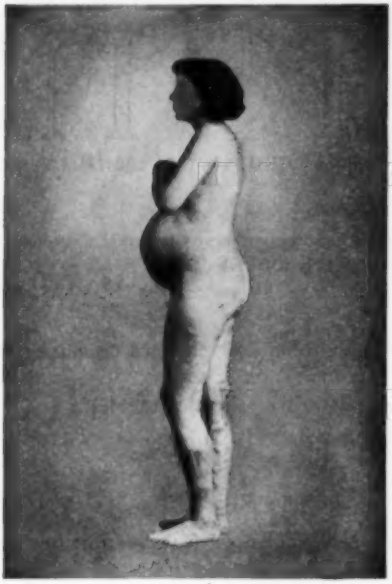
*"Gitaligin" Brand of gitalin (amorphous) is a trademark of White Laboratories, Inc.

APPROXIMATE MAINTENANCE
DOSAGE EQUIVALENTS
Ambulatory patients, 0.5 mg. Gitaligin
approximates 0.1 Gm. digitalis leaf;
0.1 mg. digitoxin; 0.5 mg. digoxin; or
1.0 mg. Lanatoside C.
Supplied as scored tablets, each tablet providing
0.5 mg. of amorphous gitalin, in bottles of 30 and 100.

Varicose Veins during Pregnancy

In estimating the value of support of the abdominal wall during pregnancy a prominent Obstetrician* states, among other items, the following: –

"By supporting the abdominal wall, it holds the growing uterus in place. Thus the feeling of weight and discomfort is lessened and, at the same time, interference with the return circulation from the lower extremities is diminished. Accordingly, edema of the ankles and varicosities occur much less frequently when a good maternity corset is worn."



• Patient 32 years old, gravida IX, para VII. Severe varicosities of both legs and vulva; noticed with first pregnancy, increasing with each succeeding pregnancy. Came to clinic when in seventh month of pregnancy.

• Same patient: No support worn in previous pregnancies. Patient states she has had some relief from varicosities since wearing the garment. Relief especially as regards tiredness; can go longer each day.

Education of mothers to see their physicians early in pregnancy is still sorely needed. Camp Supports are recommended by many Obstetricians.

**Alfred C. Beck, M.D., Obstetrical Practice, Fourth Edition, Chapter IX, Page 181, Published 1947 by The Williams & Wilkins Company, Baltimore*

CAMP Supports

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World's Largest Manufacturers of Scientific Supports

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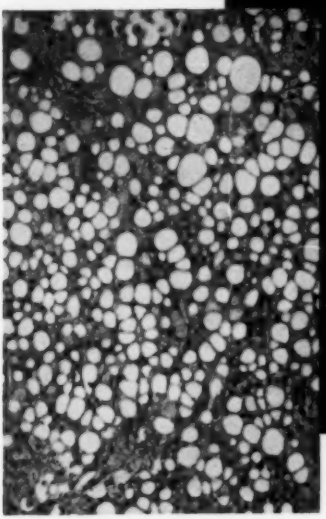
CHOLINE LIPOTROPIC ACTION

IN THE PREVENTION AND REVERSAL OF FATTY INFILTRATION



PATIENT . . . Middle aged female, with history and findings suggesting cirrhosis: loss of appetite, nausea, vomiting, vague gastrointestinal complaints, enlarged liver. Liver biopsy showed extensive fatty changes without fibrosis, indicating that the condition would be still amenable to treatment.

REGIMEN . . . High protein, high carbohydrate, moderate fat, reinforced with vitamin therapy and the lipotropic agent, *Choline (Flint)*. Patient remained ambulatory, except for short period of hospitalization required for biopsy.

RESULTS . . . At the end of four weeks' treatment, a second biopsy was taken, revealing an entire disappearance of the fatty changes. All signs and symptoms of hepatic failure had disappeared.

REMARKS . . . A successful end-result depends on early treatment of fatty infiltration during the prefibrotic stage—diagnosis at this time is governed largely by clinical signs and symptoms.

Choline (Flint) presents Choline Dihydrogen Citrate in two convenient dosage forms:

PALATABLE "SYRUP CHOLINE (FLINT)"
—one gram of choline dihydrogen citrate in each 4 cc.
Pint and gallon bottles.

CONVENIENT "CAPSULES CHOLINE (FLINT)"
—0.5 gram of choline dihydrogen citrate per capsule.
Bottles of 100, 500 and 1000.

FLINT, EATON & COMPANY
DECATUR, ILLINOIS

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

plus and minus factors

in controlling smooth muscle spasm

TRIGELMA*-H. M.

(BUFFINGTON)

antispasmodic • antacid adsorbent

plus + + +

+ Relative freedom from toxic side effects, as dryness of the throat, dilation of pupils, and increased heart rate.**

+ Synergistic antacid-adsorbent properties.**

+ Greater patient acceptability resulting from ease of administration and zesty fruit flavor.**

minus — — —

— Secondary acid rise characteristic of primary antacids.**

— Constipating effects.**

— Interference with iron absorption.**

TRIGELMA* — H.M. (BUFFINGTON) contains homatropine methyl bromide in a flavored mixture of concentrated aluminum hydroxide gel and magnesium trisilicate. Available in liquid and tablet form.

STOCKED BY LEADING WHOLESALE DRUGGISTS

** *Bibliography and Professional samples available on request.*

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PHARMACEUTICAL CHEMISTS

WORCESTER 8, MASS. U.S.A.

Haven't you forgotten something, Madam?

REMEMBERING the foods marked essential during pregnancy and lactation may be a problem for some patients, especially when adventurous appetites get the upper hand. In such cases, you can help offset "lapses" of memory by prescribing potent, convenient DICALDIMIN as a prenatal or postnatal dietary supplement. • A daily dose of from 3 to 6 easily swallowed DICALDIMIN Capsules affords a generous supply of calcium and phosphorus, plus iron, vitamin D, thiamine, riboflavin and nicotinamide in amounts considerably greater than the recommended daily allowances for pregnant women. DICALDIMIN WITH VITAMIN C offers, additionally, a protective dose (50 mg.) of ascorbic acid. For patients you suspect might "forget," why not prescribe one of these supplements? Both DICALDIMIN and DICALDIMIN WITH VITAMIN C are available in bottles of 100, 500 and 1000 capsules. Abbott

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(ABBOTT'S DICALCIUM PHOSPHATE WITH VITAMIN D, IRON AND VITAMIN B COMPLEX FACTORS)

each DICALDIMIN capsule represents:	
Dicalcium Phosphate Anhydrous	725 mg.
Ferrous Sulfate, U.S.P.	50 mg.
Thiamine Mononitrate	3 mg.
Riboflavin	3 mg.
Nicotinamide	12 mg.
Vitamin D (Viosterol)	500 U.S.P. units

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SANBORN
Poly-Viso CARDIETTE

MULTI-CHANNEL

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This new Sanborn instrument opens the way for recording possibilities in biophysical research which until now have never been made available. Four channel direct simultaneous recording with a wide performance versatility places in the hands of the "Poly-Viso" user new tools for obtaining biophysical research information in more valuable forms and combinations.

Up to four electrical or physiological phenomena may be recorded, separately or simultaneously, the channels being used either for completely different phenomena or for closely related events such as four cardiograph leads. Three types of input circuits permit the operator to record different types of phenomena such as any electrocardiograph lead, "pulse" type quantities, heart sounds for timing and other correlation, and slowly varying quantities such as blood pressures. And, according to the requirements of the events he is recording, the user can vary the sensitivities of individual channels from 1cm/1mv down to 1cm/50 volts, and choose from eight paper speeds: 50, 25, 10, 5, 2.5, 1.0 and 2.5 mm/sec.

Recording is in true rectangular coordinates — imperative for multi-channel research work — and because the quantities are directly recorded, the user can observe the recording as the events occur, making possible immediate analysis of many problems.

Design of the "Poly-Viso" is based on that of the world-wide used and accepted Viso-Cardiette described briefly below. As illustrated above, the "Poly-Viso" is completely enclosed in a mobile mahogany cabinet. It is A. C. operated throughout. *Write for the literature described in lower right corner of this page.*

FOR

SINGLE-CHANNEL

RECORDING OF ELECTROCARDIOGRAMS
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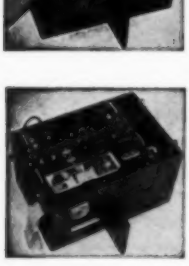

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PRESENT DAY UNDESIRABLE TRENDS IN THE TRAINING OF PHYSICIANS AND OF TEACHERS OF INTERNAL MEDICINE*

By HENRY A. CHRISTIAN, M.D., M.A.C.P., *Brookline, Mass.*

No doubt it will seem presumptuous of me this afternoon to step out of the past to criticise, even gently, the ways of what to me is the younger generation of medical folk. However, I am going to be presumptuous and develop the thesis that today the usual work program of the resident staffs of our hospitals is defective in that it does not provide in adequacy that form of training calculated to develop interns and residents rapidly and steadily into well trained clinicians, and that at this period of their development there is undesirable emphasis placed on investigation as the most important factor in the training of those who are to become in later life physicians and teachers of internal medicine. Please note that I have said physicians *and* teachers, not physicians *or* teachers, for I believe both need the same form of early training.

Until I retired 11 years ago from activity in hospital and teaching work, it had been my habit at fairly frequent intervals to look into the methods being used by my colleagues in the conduct of their clinics and departments of medicine, often visiting them on their own grounds, with the idea of adapting to my own activities what I found admirable in the local domain of my colleagues. Besides this, each year I brought into my clinic some man outstanding in medicine to live for a time with my resident staff and to conduct my wards as was his custom in his wards, thereby learning his ways of doing things.

In these ways I am sure that I made my own activities ever more stimulating to, and more effective in the training of, the young men working under my guidance, whether they were students in the medical school or members of my resident staff.

It always has been my belief that much could be learned from young men

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to whom one should look most often for new and better ways in the doing of old things, and such has proved to be the case. Probably in reverse, the eyes of an old man can see clearly and his tongue speak fruitfully to those younger and young men who now are carrying on that happy rôle—"He who teaches and yet still learns." I still believe that the best methods in guiding those commencing medicine evolve from using wisely the ideas of young men, tempered by the councils of older, even old, men like myself, councils builded on their experiences in teaching and training young men.

To get an adequate idea of existing methods being used in the training of medical graduates who will become in the future physicians and teachers of internal medicine, I have obtained the plan of organization of the resident staffs in a large number (75) of hospitals, both teaching (i.e., connected with medical schools) and non-teaching, scattered hither and yon over the United States and Canada; and from teaching hospitals I have got also their methods of utilizing and instructing students serving as clinical clerks on the wards. In addition to this, I have availed myself of numerous opportunities to have informal contact with medical students, hospital interns and residents and young instructors, who have seemed to like to visit a retired oldster and over a glass of good wine chat of medicine, old and new, and of their own activities. By these several means I have gained a considerable insight into the present day pattern of training of young men in internal medicine and of their point of view, and have found evidence of considerable dissatisfaction among young men with these methods of training. From this, quite to my surprise, I have found that there exists now almost everywhere a striking uniformity of pattern in the resident staff organization of medical clinics and in their ways of training young men, so much so that I am led to wonder what are the influences which have led to such striking uniformity, and whether, with this existing organization of resident staffs, the best possible preparation is being given to the men who will become in the future physicians and teachers of internal medicine. This I will discuss later, after having spoken of the factors that influence the young man in his selection of the type of medicine he will enter.

What are the chief influences that determine the type of training that a young man will seek following his days in the medical school, after he has determined to make of himself an internist, possibly a teacher of internal medicine? First in importance in all probability is the guidance, conscious or unconscious, of some one of his teachers with whom he has come into some considerable degree of personal contact and whose mannerisms he often has begun to imitate. Next in importance is the organization of the hospital medical clinic in which he has chosen to work, and the personality and interests of its chief and of other staff members. Then come the personality, characteristics and individual capacities and preferences of this young man himself and what he has determined on as his own particular goal in medicine. This order of relative importance may not be acceptable to all, but that is not important, if the existence of each is recognized. Of course there

are numerous other influences, which have some, possibly an important, part in this matter, which I am sure all of you will recognize, so I will not take time to name them.

What today is the general type of man who is professor of internal medicine and chief of medical clinic in the teaching hospital and consequently a—possibly the chief—influence in guiding the men who will become in due course of time physicians and teachers of internal medicine? Too often he is what can be termed a clinical scientist, not a clinician—more a specialist in some single field of internal medicine than one broadly conversant with the lore and the practice of medicine. This is particularly true of his earlier years as a professor, for many of them will become eventually clinicians rather than clinical scientists. The disadvantage of this is that, as chief of clinic, the clinical scientist is not too well equipped to give to the hospital patients the best possible type of treatment and, in my opinion, not the one likely to develop for the resident staff that form of training best calculated to develop its members into becoming superior clinicians.

Another disadvantage of this situation is that, in the eyes of the young man of today, this type of professor and chief of clinic has attained his position largely, if not chiefly, by reason of his published investigational work. At least I find that is the opinion very generally held by the young men with whom I have come into contact; and so they, seeking to imitate, primarily desire to investigate and to publish, believing that to be the surest path to academic preference, and at this early stage in their development the majority regard academic medicine as the type of medicine most to be desired. Their belief in the importance of publication in determining academic preference is fully justified by my own experience at Harvard where, in my later years, in the discussion of men proposed for promotion in clinical departments or for new posts, much more attention usually was given to publications than to evidence of teaching skill and of sound progressing knowledge of medicine; and this, I gather from conversation with colleagues in other medical schools, is by no means an unusual approach to promotions and to calls to professorship. The young man, keenly alert as to how to get along and believing that is the way, seeks chiefly to investigate and to publish, possibly even stressing the latter, since he thinks a bibliography of numerous titles will have much weight in the consideration of his promotional advancement. So far as possible, if he has the chance, he will select an appointment on the resident staff of a clinic in which he believes investigation is the major aim.

Publication and the developing of a personal bibliography, besides so often being a major interest to the young man, seem to me to have become almost a game or racket utilizing devices to gain multiplicity of published papers. I note the frequent device of subdividing publication into parts, separately published under individual titles. This has the advantage of creating the impression of a seemingly great activity in investigation, and since, as a rule, only Part I reviews the work of others, those who read the subsequent, separately published parts get the idea of an unjustified orig-

inality. This subdivision into parts actually is an old game and so probably not as effective now as formerly. A more recent device is multiplicity of authorship, so that many can get into recorded literature and seem to appear as investigators. One now sees in our journals papers with a half-dozen or even a dozen or more authors to a single paper, so that all who participated in any way in the mechanics of the study will seem to be the originator of the new idea, if there is one in the paper, and often that proves difficult to find. Since "et al." or "and others" after the first name is now almost necessarily the adopted way to refer to such papers, it would seem that "et al." is going to become in the future the most prolific contributor to medical literature as recorded in our indexes and bibliographies. The next possible step to be taken may be to put on as authors all the personnel of the laboratory or even of the clinic, which to me would be a reductio ad absurdum of this race for investigational publicity but not very much worse than this present day multiplicity of authors of published papers.

Next in order of importance of the influences which I have already cited comes the actual organization of the clinic in which the potential physician and teacher of internal medicine is to get his early training. Here he has very little choice because, with extremely few exceptions among the 75 hospitals from which I secured data as to the organization of resident staff, organization has been stereotyped into a pattern within which there seems to be remarkably little variation. This pattern is usually a one-year internship (occasionally two years) followed by one to three years of residentship. The internship is of three types: (1) a rotating service (in 43 of 75 hospitals) including, besides medicine, surgery, obstetrics, pediatrics, and medical and surgical specialties with varying lengths of time (two to four months) on the medical wards; (2) a straight medical service, i.e., with at least 12 months on the medical wards (in 22 of 75 hospitals), and (3) a mixed medical service (in 10 of 75 hospitals), i.e., with six to nine months on the medical wards and the remaining of the 12 variously divided among such medical specialties as dermatology, neurology, psychiatry, pediatrics, syphilis, tuberculosis, diabetes, cardiology, endocrinology, etc.—of course no service giving time on wards devoted to more than two or three, possibly four, of these. The resident's work also is usually divided up into varying patterns of service in medical specialties, in bacteriology and pathology and in different laboratory technics, with quarter to half-time for direct study of medical patients and a varying time available for participation in investigation, with the result that too little time is spent in continued study of patients. The rotating internship preponderates—in fact, is almost the rule—in non-teaching hospitals (21 out of 23); it is required for registration in medicine in 13 states. In other words, so far as organization of resident staff is concerned, this young man will have rather little choice; any one of many medical clinics in which he might choose to work as a member of the resident staff will put him through about the same general mechanism of training, and he might just as

well go into any one of them. The unusual man probably will try for the very infrequent clinic that is different.

With very few exceptions, all interns for a given year seem to begin work on the same day, and their work is in no fashion graded or progressive. Interestingly, this fact seems a direct violation of the requirements of the American Medical Association for a hospital to be rated as satisfactory for internships and so marked by an "*" in the annual report on hospitals in the *Journal of the American Medical Association* (J. A. M. A., 1949, May 7, p. 37). The wording of this requirement is that "there should be a progressive increase in the intern's responsibilities" (J. A. M. A., 1949, Sept. 3, p. 52), which would seem almost an impossibility when all start their service on the same day, and yet it is a most necessary factor in training young men to become competent clinicians.

Also, that the 12 months' period of internship is not really satisfactory is evidenced by this pronouncement by the A.M.A.: "An interneship should be of not less than twelve months' duration. Longer periods of service are preferable because they permit a more satisfactory educational program and allow the interne sufficient time in which to be trained adequately to assume increasing responsibility in various fields of medicine." I wonder why this deficiency in meeting the A. M. A. standards in one respect, and failure to give more than the minimal of acceptable time rather than the advised longer time, have been allowed. This I can not answer, not being a member of the committee of the A. M. A. that passes on hospital qualifications for acceptability.

One can size up the present situation in resident staff organization by saying that there is today great uniformity in the organization of resident staffs in American hospitals. However, my observation of standardization in the field of medicine, as well as elsewhere, is that as a rule standardization begets uniformity, and uniformity with few exceptions means Mediocrity, Mediocrity spelled with a very big "M." This is because uniformity in anything is attained by the dual process of scaling-up the inferior and scaling-down the superior—or at least that is what ordinarily happens. So it is my feeling that today, with few exceptions, resident staff organization in American hospitals has attained not only uniformity but mediocrity, and is not one that is bringing to those holding posts under it the best possible training for the young men who will become our future physicians and teachers of internal medicine. Why does this pattern of organization exist so generally? What are the influences responsible for it? Why does it persist? Naturally these questions come to your mind; later on I will attempt to answer them.

Before doing this, however, I will take up the third of the influences that have played a part in determining the type of training that the young man will need in his development. This I put down as the personality, characteristics, and individual capacities and preferences of the young man

himself and what he has determined on as his own particular goal in medicine. Obviously these must play an important rôle in determining whether in the future he will become internist, surgeon, obstetrician, or some other type of practitioner or teacher, or whether he will enter some of the basic medical sciences. The important thing here is whether, on the basis of these individual characteristics, he will select for himself the suitable branch of medical activity. Such consideration seems outside of what has been chosen as the subject of this paper and will not be given any further consideration here.

Let us turn now to consideration of what appear to have been the causative influences in the development of present day conditions in internal medicine in relation to the training of the future physician and teacher of internal medicine, conditions which, as I have already stated, do not seem to me to provide satisfactory training at the level of the resident staff in even very good hospitals.

It seems to me that five influences have been important in determining the present almost universal pattern of resident staff organization in our American hospitals. These are: (1) standards set by the A. M. A. for acceptability of a hospital for internship, modified or not by state laws, which in some instances specify the character of the service of the intern; (2) the requirements of the Board of Internal Medicine for admission to its examinations and for eventual certification; (3) the influence and policy of the chief of the clinic (in teaching hospitals, a professor in the affiliated medical school); (4) a carry-over from the necessity for hurried hospital training to meet the demand for medical men in the armed services in World War II; and (5) the natural tendency of young men to get finished as soon as possible all fixed requirements of their training.

Of these influences, the A. M. A. and the Board of Internal Medicine obviously are the most important. So far as they go, they are "musts," since, unless their minimal standards are accepted and followed insofar as they are in actuality required and checked on, no hospital will be rated as acceptable for internships, and no graduate in medicine in the future will be certified as an internist by the Board of Internal Medicine; and without this certification no one will be certified subsequently by any one of the subsidiary boards of the several specialties of internal medicine. No one can object to these boards' setting a minimal requirement, but one wonders why the A. M. A. specification for a progressive increase in the intern's responsibilities is not enforced, and why our hospitals almost to a man are satisfied with the minimal requirements of these two agencies and are not stimulated to follow their suggestions for advance beyond the minimal. Both agencies are, I think, open to serious criticism on these accounts.

As to influence (3), that of the chiefs of clinic staff, this appears to be almost negligible. Were that not true, it seems inconceivable that resident staffs would have almost universally in their required work nothing more than the minimal requirements of these two boards. Obviously, a chief

of staff is completely at liberty to lengthen and to change the character of the work of his interns and residents so long as he maintains the minimal requirements of the A. M. A. and Board of Internal Medicine. Since you can count almost on one hand the chiefs who have done this, most chiefs must be satisfied to apply only minimal requirements, and so, in the last analysis, they are responsible for what I consider an undesirable type of resident staff organization, undesirable because it is not training adequately men needed in the future as clinicians in the category of physicians and teachers of internal medicine.

Can it be that influence (4), a carry-over from war time necessities of a shortened period of hospital residency, still is effective? It is a fact that, after military necessity had shortened internships to nine months, with half of the interns given nine additional months as assistant resident, very many hospitals with the end of military requirements failed to return to their previous plan of graded service with increasing responsibilities over a time longer than 12 months on the medical wards, often at that prior period a total service as intern of 16, 18 or 24 months. Is this an expression of inertia, or one of satisfaction in fulfilling only the minimal requirements of the A. M. A. and the Board of Internal Medicine, or possibly both? This to me is something that chiefs of medical staffs should ponder over.

Influence (5), the tendency of young men to finish a set task as rapidly as possible, indirectly may be important in popularizing those hospitals with resident staff organization entailing the fewest years which will get these young men by the requirements of state Boards of Registration and the Board of Internal Medicine. However, there is no need for hospitals to popularize themselves in relation to filling posts on their resident staffs because there are more internships seeking incumbents than there are available recent graduates in medicine to fill them. Internships are now a glut on the market, with many unfilled, particularly in nonteaching smaller hospitals, many of which are capable of giving very well the training needed by the young graduate.

If the present day situation as regards organization of resident staffs in American hospitals is unsatisfactory, as I believe it to be, on whom should the chief responsibility be placed? I would say, on the Board of Internal Medicine and on the chiefs of medical staffs: on the first for setting a too short minimal intern requirement instead of insisting on a longer one with much permitted elasticity, and on the second for inertia or lack of concern. As to the second, the chiefs of medical staffs seem to have almost complete freedom of action, certainly in the teaching hospitals, as already has been stated.

What has happened appears to me to bear out in some considerable degree the objections to the Board of Internal Medicine raised in 1937 by the late Dr. Thomas R. Boggs, of Baltimore, who took for the subject of his presidential address before the Association of American Physicians, "Regimentation in Medicine," and among other things therein stated: "This

standardization with excellent ideals as its rallying point may yet contain in its logical development methods which can but lead to a bureaucratic stereotypy of form far worse than the evils it is set up to correct. . . . The training of the qualified internist may be obtained in a variety of ways, and it is desirable and to the public interest that this should be encouraged rather than to try to reduce it to one prescribed, specific mode. . . . The trend of the plan seems on close inspection to contain possibilities of method which strike at the very roots of medical education by substituting the extralegal demands of certificating bodies for the considered plans and policies of those properly entrusted with medical education and training."

What is needed, in my opinion, to improve vastly the training value of positions on a resident staff from the point of view of developing a better physician and teacher of medicine can be reduced to simple terms: first, to carry out in extenso what is expressed in the A. M. A. requirement for acceptance of a hospital for internship, namely, that "there should be a progressive increase in the interns' responsibilities"; and, second, to lengthen the period of internship to 16, 18 or 24 months, followed by a period as assistant resident and, if possible, as resident, with terms of internship commencing not all on one day but scattered through several different months in the year. If the service is a rotating one, its first period should be one in which there is a graded progression of responsibility—preferably, perhaps, in medicine,—before going on to the various other required services, such as obstetrics, surgery, pediatrics, etc., with a final period as assistant resident in medicine or in any other of the fields of medicine as the intern selects.

For medicine, I would suggest in very general terms some such plan as the following for what I term a graded straight medical service as intern.*

(1) Four months doing chiefly routine laboratory studies and learning how to do other of the more complicated ones; and taking over under guidance, chiefly of the junior intern, some of the history taking and physical examinations on patients, while being present at ward rounds at which he reports on his laboratory work on each patient.

(2) Four months as junior intern, chiefly concerned in history taking and physical examinations of patients, with some of the direction of treatment under the guidance of the senior intern whose work he will take over when the senior is off duty.

(3) Four months as senior intern, when he will do some history taking, but will be concerned chiefly with physical examinations, planning and ordering laboratory studies, and ordering and directing treatment, all under supervision chiefly by an assistant resident and the resident. For efficiency, it is desirable that all directions and orders pass through the senior intern to avoid any confusion or duplication, thus making of the senior the responsible director of the care of patients on his ward. Special patients

* Various committees and individuals also are recommending the general adoption of a two year internship as a means of meeting the present situation in which so many hospitals are unable to get the needed number of interns.

should in this same way be under the senior, who will be responsible for ordering and carrying out all examinations and forms of treatment desired by the one making special studies. All three of these interns should go on all ward visits, receiving instructions, directions and criticisms from the visiting physicians or physicians on duty, one of whom should be making the regular ward visit.

(4) Finally, four months in the medical out-patient department, where he will be responsible for the examination and care of ambulatory medical patients, taking charge of them as a practicing physician would take charge of office patients, acting on his own responsibility but using, in the capacity of consultant, assistant residents, resident physician, and members of visiting staff, chiefly those with offices in the hospital. This plan obviously can undergo many modifications to fit local conditions, provided only that the principle of graded progression in activity and responsibility is preserved. House officers should supervise the work of student clinical clerks, who in a sense are their assistants.

If there is a rotating service, this general plan of progressing responsibility can and should be put into effect, with various periods of the total service assigned to the various subdivisions of the hospital service in relation to the total period of the internship and to whether the individual intern subsequently will become assistant resident in medicine, surgery, obstetrics, pediatrics, etc.

In such an arrangement of intern service there will be very little opportunity for any sustained investigation. Investigation is not a needed factor in this stage of the training of the future physician and teacher of internal medicine, but should have a place in the plan of work of assistant residents and resident.

It is my belief that an internship of more than 12 months (preferably two years) is needed to qualify the men for beginning an assistant residentship, unless in the first year as assistant resident the work actually is of the nature already described for the senior intern. This is a device adopted for medicine in some hospitals, particularly where the internship by state law is required to be a rotating one and has been of 12 months' duration. Actually, this is an internship of 24 months, even if in the second year it has been called an assistant residentship. This should not be accepted as one year of assistant residentship in the requirements of the Board of Internal Medicine. Why do I make the statement in the first sentence of this paragraph? It is because, in the earlier years of development at the Peter Bent Brigham Hospital in Boston, I found by trial that those men who had had only a 12 months' internship, whether straight medicine or rotating, did not prove capable of getting the most for themselves out of an assistant residentship. Soon I said to such men that I would not take them on as an assistant resident unless they were willing to come as intern, beginning at the bottom of that service and remaining for 16 months in it, which was the length at that time of my internship. A number of men did this and later

told me how sound was my attitude, for they realized that they could not have got in training out of their assistant residentship what they did get after having taken the complete internship as we gave it.

Now a few words as to the assistant residentship. This should be for not less than two or three years, one year of which, wisely or unwisely, now is permitted by the Board of Internal Medicine to be the second year of an approved internship. The duties should be of progressing responsibility and, except for the year permitted to count as a second year of internship, of varying activity, with about half time given to different activities in connection with the care of patients and about half time allotted to investigation. These activities should not involve frequent shifts in character and place of work.

I am old fashioned enough to decry assigned, planned investigation, but believe each man should find his own problem and be aided by suggestions as to methods of procedure. If a man in the period of residentship does not find a problem for investigation, this time can be spent just as effectively, so far as his training is concerned, in more prolonged clinical study of patients or in library reading or in bacteriology, pathology, chemistry, etc., where he may do profitably routine rather than investigational work. Certainly that was my experience at the Brigham Hospital.

In residentship there should be time allotted to supervision of interns' and students' work. Both interns and residents should participate actively in the various conferences and in discussional and teaching exercises, but the number of these should not be so great as often seems to be the case: when there are very many of them, there is too little time left for other and more important work.

It is highly desirable for the training of these young men that at some time they spend, if possible, one or even more years in a laboratory of a basic or preclinical science such as physiology, biochemistry, pathology, pharmacology, bacteriology, etc. presided over by a master in his field. The most important criterion of selection should be not the subject but the mastership of the head of the laboratory. It is well to remember that laboratories of the clinic almost always represent applied, not basic, science and will not have a master in their charge, directing and inspiring the young, as will be found in a university or medical school department of a basic science.

This suggested plan of organization of the resident staff, however, will not attain the desired end of satisfactorily training men to be fine clinicians unless the clinic places patients and their care as the first obligation of the clinic and of all connected with it. Only when patients are receiving the best possible treatment, with every possible consideration given to their needs and preferences, should any other of the activities of the clinic, such as teaching and investigation, be undertaken. No one who does not put the patient's interests first, from chief all the way down to the beginning intern, should be even tolerated in any clinic. Nothing ever should be done in the study and investigation of patients not considered to be primarily

important in the treatment of the patient, without careful explanation of it to the patient and without obtaining his expressed consent to its being done. This is particularly essential in any study that is likely to be uncomfortable or fatiguing to the patient; obviously none should be allowed which might be injurious to the patient or leave any persisting damage. Every chief of clinic should be held responsible, in the sense just expressed, to carry out the all-desirable motto: "The interest of the patient always comes first." The chief who is truly a clinician will do this spontaneously, and his influence will be felt by all working in his clinic.

Such was William Osler, my own teacher, a master clinician, who has told us: "In the natural method of teaching, the student" (and this applies also to intern and resident) "begins with the patient, continues with the patient and ends his studies with the patient using books and lectures as tools as means to an end. . . . The art of the practice of medicine is to be learned only by experience; 'tis not an inheritance; it can not be revealed. . . . Medicine is learned by the bedside and not in the class room. . . . Live in the wards. Do not waste the hours of daylight [on that] which you may read by night. . . . To study the phenomena of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all. . . . I fear lest the broad open spirit . . . should narrow as student and teacher chase each other down the fascinating road of research, forgetful of those wider interests to which a great hospital must minister."

In conclusion I say: Plan the work of the hospital's resident staff to accord as far as possible with these wise words of Osler, and then once again we will have young men well prepared to be physicians and teachers of internal medicine.

Summary

I have developed the thesis that at present the usual work of members of the resident staffs of our hospitals is defective in that it does not provide in adequacy that form of training calculated to develop interns and residents rapidly into well trained clinicians, and that at this period of their development undesirable emphasis is being placed on investigation as a most important factor in their training. In a study of the resident staff organization in 75 teaching and nonteaching hospitals I find almost total uniformity, and point out that uniformity usually is based on scaling up the inferior and scaling down the superior, with resultant mediocrity.

I have enumerated and discussed the influences that determine the type of training the young man will seek after his medical school graduation to make of himself a physician and possibly a teacher of internal medicine, and also the influences which appear to me to have resulted in this almost total uniformity of organization of resident staffs. I have outlined what to me seems to be an organization of resident staffs more likely to produce a better type of clinician because it emphasizes progressive increase in responsibilities under the guidance of superiors.

THE BACTERICIDAL ACTION OF PENICILLIN IN VIVO: THE PARTICIPATION OF THE HOST, AND THE SLOW RECOVERY OF THE SURVIVING ORGANISMS *

By HARRY EAGLE, M.D., RALPH FLEISCHMAN and ARLYNE D. MUSSELMAN, *Bethesda, Maryland*

ALTHOUGH penicillin is known to be actively bactericidal, there is reason to believe that its therapeutic activity is not determined solely by that direct bactericidal action, and that other factors may supervene in vivo. Thus, Jawetz [9] found that, in a mouse streptococcal infection bacteria continued to die long after penicillin in demonstrable amounts had disappeared from the serum; and clinical experience has established the fact that penicillin is effective even when given so infrequently that for a considerable period between injections it is not present in bactericidal concentrations.[11, 12, 13, 14] These observations would seem to minimize the importance of the concentration of penicillin in the body fluids. On the other hand, it has been shown in previous studies from this laboratory (*a*), that the concentration of penicillin necessary to initiate a bactericidal effect in vivo is essentially the same as that which is similarly effective in vitro [8]; (*b*), that organisms previously exposed to high concentrations of penicillin are not thereby sensitized to the action of the drug [8]; and (*c*) that in experimental infections treated with penicillin there is a close parallelism between the aggregate time for which penicillin remains at bactericidal levels and the therapeutic efficacy of the particular schedule.[5] Further, it has been generally found that organisms which are killed only by high concentrations of penicillin in vitro require similarly large doses of penicillin in vivo.

The experiments to be here described were undertaken in an effort to resolve these apparent contradictions by following the course of the bactericidal action of penicillin in vivo in relation to its concentration in the serum. Data are also presented with respect to the slow recovery of the surviving organisms after the disappearance of penicillin, the continuing death of certain bacterial species as an aftermath of their exposure to the drug, and the quantitative importance of the latter phenomenon relative to the direct bactericidal effect of penicillin. The implications of these observations with respect to the therapeutic use of penicillin are discussed in the text.

METHODS AND MATERIALS

1. The four strains of bacteria used in the present experiments were *Diplococcus pneumoniae* type I, *Diplococcus pneumoniae* type III, a group A β-hemolytic strepto-

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coccus (C–203), and a group B β-hemolytic streptococcus. These strains were first passed through mice (five times weekly) for three weeks. Thereafter, the virulence was maintained by similar passage through mice twice weekly.

2. Bactericidal action of penicillin and recovery of organisms in vitro. The technics used to follow the bactericidal action of penicillin quantitatively, and to follow the slow recovery of the organisms after the removal of the penicillinase, have been described in detail in a preceding paper.[3]

3. *The fate of penicillin-treated bacteria in vivo.* Mice weighing 17.5 to 22.5 gm. were inoculated intramuscularly with a measured number of organisms.

(*a*) In the experiments in which normal bacteria were inoculated and the animals then treated with penicillin, a culture in the logarithmic phase of growth was diluted to contain 200,000 organisms per c.c. as determined by microscopic count,[4] and 0.1 c.c. (20,000 organisms) was inoculated intramuscularly into a thigh muscle. Somewhat larger inocula, up to 200,000, were used in a few experiments. The mice were then immediately treated in the opposite leg with a single intramuscular injection of sodium penicillin G in varying dosage, also in a volume of 0.1 c.c.

(*b*) In the experiments in which the organisms were exposed to penicillin in vitro prior to their inoculation, a culture in the logarithmic phase of growth was diluted to contain 2 to 5 million organisms per c.c. by microscopic count, and the number of bacterial chains or clumps determined by plate count. The suspension was then exposed to 0.1–0.15 μg./c.c. of penicillin at 37° C. for a period of one to three hours as indicated in the tables or figures. Penicillinase (Schenley "S") was added to a final concentration of 10 "units"/c.c. in order to inactivate the penicillin.* An aliquot portion of the penicillin-treated suspension was then replaced at 37° C. in order to follow the in vitro recovery of the organisms by plate counts at the intervals indicated in the tables. Mice were at once inoculated intramuscularly with 0.1 c.c. of the penicillin-treated suspension.

In both types of experiment, at varying intervals after inoculation, the inoculated muscle was removed from groups of mice, emulsified in a Waring blendor in 50 c.c. of 1 per cent rabbit blood-broth, and the number of surviving organisms was determined by plating out in blood agar. Three c.c. of the muscle emulsion were placed in 8.6 c.c. of beef heart infusion agar, and 0.4 c.c. of defibrinated rabbit blood containing one-twentieth part of 10 per cent clarase (Takamine) was then added, the clarase serving to inactivate any residual penicillin. When large numbers of organisms were anticipated, one, two or three serial 40-fold dilutions were made by transferring 0.3 c.c. into another tube containing 11.3 c.c. of infusion agar and 0.4 c.c. of blood.

The number of organisms recovered from the muscle immediately after inoculation was often higher than the number contained in the original culture dilution used as inoculum. This paradoxical increase varied from 10 to 200 per cent in individual mice, and reflected the break-up of small chains of bacteria when the inoculated muscle was emulsified in the blendor. In calculating the percentage of organisms surviving in the muscle at varying intervals after treatment, the number of colonies appearing in the subculture of the tissue emulsion was referred to the number recovered immediately after inoculation as 100.

Under the impact of penicillin in vivo, the organisms stopped multiplying and remained in the inoculated muscle. Only occasionally could organisms be found in the lung, liver or spleen during the time of the experiment, and then their number was insignificant in relation to the number present in the muscle. (This was true also when penicillin-treated bacteria were inoculated.) Even after the penicillin had disappeared, and after the surviving bacteria had recovered from its toxic effects to resume multiplication at a normal rate, many hours usually elapsed before the number of bacteria in the blood or in the other tissues tested became significant in com-

* The courtesy of the Schenley Laboratories in providing the large amounts of this material used in the present experiments is gratefully acknowledged.

parison to the number present in the inoculated muscle. After the first few experiments, subculture of tissues other than the inoculated muscle was therefore discontinued.

In the experiments designed to determine the effect of exposure to penicillin on the virulence of these strains, serial 10-fold or 3.2-fold dilutions were prepared of (1) the original culture used as starting material, (2) the same culture immediately after exposure for one to three hours to maximally effective concentrations of penicillin, and (3) the penicillin-exposed organisms after they had been allowed to recover at 37° C. for the varying time periods indicated in the tables. Twenty-five mice were inoculated with each dilution in order to determine the LD_{50} inoculum. All dilutions (in blood broth) were kept chilled during the period of inoculation in order to prevent either the multiplication of the normal bacteria, or the recovery of the penicillin-damaged organisms.[3] The number of viable bacterial clumps inoculated was determined by plate counts. It must be emphasized that these counts represent the number of viable bacteria clumps or chains, and that the number of individual bacteria may have been a small and variable multiple of that count. Within a single experiment, however, that multiplying factor would be reasonably constant.

Experimental

I. The Behavior in Vivo of Bacteria Previously Exposed to Penicillin in Vitro

When bacteria are exposed to effective concentrations of penicillin in vitro, and if the drug is removed or inactivated before all the organisms have been killed, the surviving bacteria do not immediately resume multiplication. There follows instead a period in which the number of organisms remains essentially unchanged, and during which the organisms are presumably recovering from the toxic effects of the drug. At the end of this recovery period, the bacteria resume multiplication at a normal rate.[1, 2, 3, 17]

When such penicillin-damaged bacteria were injected intramuscularly in mice or intratesticularly in rabbits, there was the same delay in the resumption of multiplication as had been observed in vitro. As is shown in figures 1, 2, 3, 4 and 5, with all four bacterial species here studied, the duration of this recovery period in vivo (bottom half of figures) was usually even longer than the recovery period in vitro (upper half of figures), ranging between four and eight hours. This explains the fact that, in the treatment of experimental infections with these organisms, a penicillin-free interval of several hours between injections did not adversely affect the outcome of treatment.[5, 6, 7] For at least this period of time the organisms were not multiplying, and only when that penicillin-free interval was unduly prolonged did the organisms recover and resume multiplication. This then necessitated the administration of larger doses of penicillin, i.e., the provision of effective concentrations of penicillin for a longer aggregate period.[5]

1. *Increased Susceptibility to the Host of Penicillin-Treated Group A and Group B β-Hemolytic Streptococci.* The mouse normally has little or no protection against these organisms (after their virulence has been exalted by serial animal transfers). The LD_{50} dose on intraperitoneal inoculation was on the order of one or two organisms, and even on intramuscular inoculation the LD_{50} inoculum usually varied between one and 20 bacteria.

However, if the bacteria were first exposed to penicillin and then inoculated intramuscularly in mice, or intratesticularly in rabbits, the organisms were found to have been rendered more susceptible to the host defense. The number of viable organisms decreased progressively for a number of hours, until the bacteria had recovered sufficiently to resume multiplication; * and

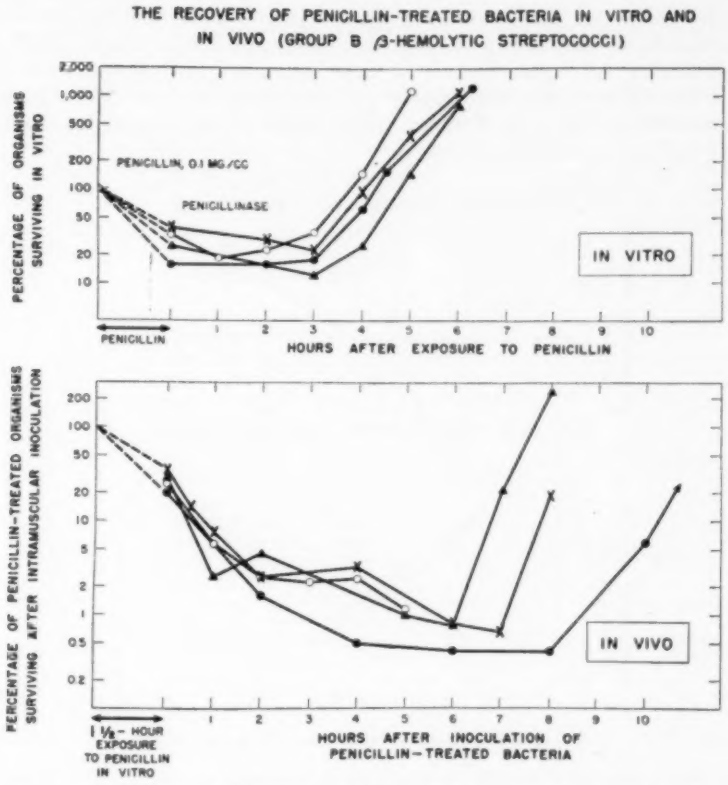

FIG. 1. The recovery of penicillin-treated Group B β-hemolytic streptococci in vitro and in vivo (mouse muscle). Summary of four experiments carried out at different times: for details of procedure, cf. page 545 and legend to figure 5. Each point in the bottom half of the figure represents an individual animal sacrificed at the indicated time after inoculation.

* This initial decrease was due to the destruction of the organisms in situ, and not to their migration or transport from the inoculated muscle into the blood or other tissues. (*a*) Viable organisms could not be recovered from the blood, liver, lung or spleen. (*b*) Penicillin-treated organisms which were not susceptible to the host (cf. experiments with pneumococci, page 554) remained essentially constant in number for the entire duration of the recovery period. (*c*) Even when normal bacteria were inoculated intramuscularly in mice, the rapidly multiplying organisms remained in the muscle for many hours, and only insignificant numbers could be found in the blood, liver, lungs or spleen (cf. page 546). (*d*) The drop in the number of organisms in the muscle was paralleled by a quantitatively equal increase in the number necessary to cause a fatal infection.

it was necessary to inject correspondingly more organisms in order to produce a fatal infection.

Four experiments with the group B streptococcus here used are summarized in figure 1. When this strain was exposed to penicillin for one and one-half hours in vitro, the surviving organisms showed the usual recovery period of three hours, after which they remultiplied at a normal rate (upper section of figure 1). However, when such penicillin-damaged bacteria were inoculated intramuscularly in mice, the number of viable organisms fell off progressively for a period of six to eight hours, and only then did the bacteria recover to resume multiplication (lower section of figure 1).* During the recovery period 98.6 to 99.6 per cent of the viable organisms inoculated were apparently killed by the host.

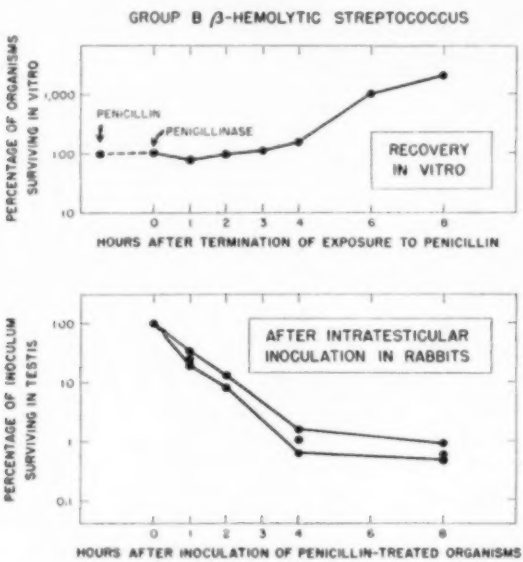

FIG. 2. The fate of penicillin-treated Group B streptococci in vitro and after intratesticular inoculation in rabbits. A bacterial suspension in the logarithmic phase of growth was diluted to contain 5×10^6 organisms per c.c. in blood broth containing sodium penicillin G in a final concentration of 0.1 microgram/c.c. After one and one-half hours at 37° C. (when none of the organisms had as yet been killed), penicillinase was added and the mixture replaced at 37° to follow the recovery and remultiplication of the organisms in vitro (top curve in figure). Immediately after the addition of penicillinase, 0.2 c.c. was inoculated intratesticularly into a total of 14 rabbits. At the intervals indicated in the figure, the inoculated testis was removed, emulsified in a Waring blendor, and the number of organisms determined by plate count. Each point in the figure represents an individual animal, and the lines are drawn through extreme values to indicate the range of variation. In three control rabbits, plate counts on the testis immediately after inoculation were 142, 144 and 100 per cent of the counts obtained on the equivalent amount of bacterial suspension (cf. page 545). In the figure the percentage of organisms surviving in the testis is referred to the average number recovered immediately after inoculation as 100.

* See * on preceding page.

TABLE I

The Effect of Exposure to Penicillin on the Virulence of a Group B β-hemolytic Streptococcus for Mice

A 2-hour culture was diluted in penicillin-blood broth to give a suspension containing 10 million organisms per c.c. (microscopic count) in sodium penicillin G at 0.1 microgram/c.c. There was an average of 7 organisms per chain in the original culture, and the plate count on the final mixture was 6.8 million per c.c. After 1.5 hours at 37° C., the penicillin was inactivated by the addition of 10 units/c.c. of Schenley penicillinase A. The tube was then replaced at 37°. At the intervals indicated in the table, mice in groups of 25 were inoculated intramuscularly with 0.1 c.c. of varying dilutions of the bacterial suspension. The number of viable organisms (actually, number of viable chains or clumps) was determined by plate counts at the time of inoculation.

Duration of Exposure to Penicillin (0.1 μg./c.c.), hours	Time Allowed for Bacteria to Recover from Toxic Effects of Drug[2]	Surviving Viable Organisms		Virulence of surviving organisms		
		$\times 10^6$ per c.c.[3]	% of Original Number	No. Inoculated[3,4]	Proportion of Mice Dying within 14 days	No. of Viable Organisms Necessary to Kill 50% of Animals[3]
0	0	6.8	100	680 68 6.8 0.68	25/25 18/25 7/25 1/25	19±6
¾	0	10.5	154	10,450 1,045 105 10.5	22/25 23/25 15/25 3/25	100±34
1½	0	8.3	122[1]	83,000 8,300 830 83 8.3	16/25 15/25 5/25 1/25 0/25	11,500±5,500
1½	1	7.0	103	7,040 704 70 7	16/25 2/25 1/25 1/25	5,000±3,200
1½	2	6.7	98	6,700 670 67 6.7	8/25 6/25 3/25 2/25	>6,700 (approx. 10,000)
1½	3	6.4	94	640 64 6.4 0.6	18/25 5/25 2/25 0/25	230±92
1½	4	6.6	97	660 66 6.6 0.7	21/25 12/25 8/25 2/25	40±19

[1] Although no significant proportion of the organisms had been killed after 1.5 hours' exposure to penicillin, they had been damaged to the extent that after the removal of penicillin with penicillinase they did not resume multiplication for more than 4 hours. With further exposure to penicillin, the number of viable organisms fell off progressively to 700,000/c.c. (10%) after 3 hours, and to 36,000/c.c. (0.53%) after 7 hours.

[2] Determined by plate counts.

[3] At inocula of less than 6 viable organisms, the number of animals inoculated was corrected for the probable number which received no organisms. The geometric mean number of bacteria inoculated into mice receiving at least one organism was taken as the inoculum in calculating the LD_{50} dose. The LD_{50} inoculum and its standard error was calculated either by Kärber's procedure or by the maximum likelihood procedure carried through 1 or 2 cycles of computation, as indicated.

Similar experiments in rabbits inoculated intratesticularly were obscured by the fact that even normal organisms grew out in the testis only after a period of several hours, due either to the ready migration of some of the multiplying bacteria, or to an actual lag in multiplication. However, when penicillin-treated streptococci were similarly inoculated, the number of viable organisms promptly began to decrease, and continued to fall off for a period of six to eight hours (cf. figure 2). In two experiments carried out at different times, 96 and 99 per cent of the organisms had disappeared from the inoculated testis in that period of time, presumably killed by the host defenses, and only after that interval did the surviving organisms begin to remultiply.

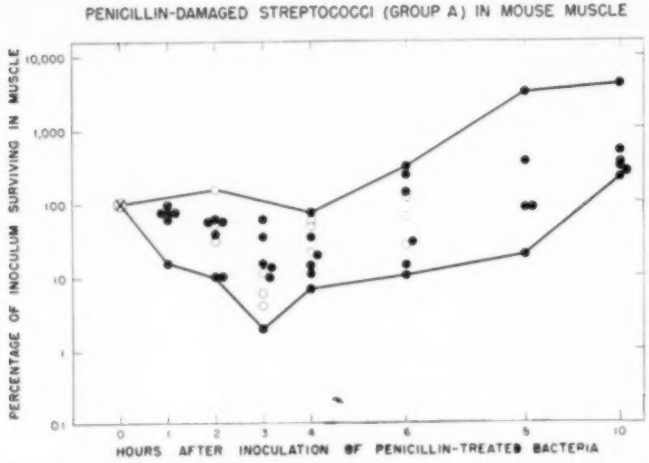

FIG. 3. The fate of penicillin-damaged Group A β-hemolytic streptococci in vitro and in vivo (mouse muscle). Summary of two experiments carried out at different times: for details of procedure cf. page 545 and legend to figure 5.

It is apparent from figures 1 and 2 that the mouse or rabbit host continues to dispose of these penicillin-damaged streptococci for a much longer time than is required for their recovery and remultiplication in vitro. At least three possible explanations may be suggested: (1) a host factor, acting on the organisms, may interfere with or delay the reparative process; (2) the host tissue may be deficient in certain metabolites necessary for the recovery of the penicillin-damaged bacteria *; or (3) the change in the organisms produced by the action of penicillin which makes them vulnerable to the host may persist beyond the time that the organisms resume multiplica-

* The recovery period may be similarly delayed in vitro by placing the organisms in an insufficiently enriched medium,[8] and in certain media the penicillin-damaged bacteria may show a progressive loss of viability resembling that which occurs with some bacterial strains in vivo.

tion. Under such circumstances, the continuing death of some of the bacteria may mask the fact that others are multiplying.

The increased susceptibility of these penicillin-treated bacteria to the host was further shown by their strikingly decreased virulence. In the experiment of table 1 (cf. also figure 6), the LD_{50} inoculum of the normal streptococci on intramuscular injection in mice was 20 organisms. After the organisms had been exposed to penicillin at 0.15 μg./c.c. for one to one and one-half hours, and despite the fact that only an insignificant proportion of the bacteria had been killed by that exposure, the LD_{50} inoculum was increased five hundred fold, to approximately 11,000 viable bacteria. When the penicillin was then inactivated with penicillinase the virulence gradually returned to normal, the LD_{50} inoculum decreasing to 230 organisms after three hours' recovery at 37° C., and to 40 organisms after four hours. Despite the small slope of the dosage-response curve, and the large error of these LD_{50} estimates, the difference in the virulence of the normal and penicillin-damaged organisms is statistically significant. A second experiment with qualitatively similar results is summarized in table 2 and figure 6.

TABLE II

The Effect of Exposure to Penicillin in Vitro on the Virulence of Streptococci and Pneumococci in White Mice

(Summary of all experiments. For illustrative protocol, cf. table 1)

Organism	Experiment No.	Minimum Lethal Dose[1] (LD_{50}) of						
		Normal Bacteria	Bacteria Immediately after Exposure to 0.1 g./c.c.		Bacteria Allowed to Recover from Toxic Effects of Penicillin for			
			Duration of Exposure, Hours	LD_{50} Inoculum	1 hr.	2 hrs.	3 hrs.	4 hrs.
Group A Streptococcus	1	4.2±1.4	1	64±32		35±9		1.4±1.1
	2	5.1±1.1	1½	250±140			<2[2]	
Group B Streptococcus	1	19±6	¾	100±34				
			1½	11,500±5500	5600±3200	>6700	230±92	40±19
	2	15–20	3	4000±2200	280±130	27±14	6±3	2.6±0.7
Diplococcus pneumoniae Type I	1	1.53±0.96	1½	15±3.5		4.1±1.1		2.6±0.7
Diplococcus pneumoniae Type III	1	<2[2]	1½	6±[3]	5.2±2.4		<2	
	2	<2[2]	1½	<2	<2	<2		<2

[1] The number of organisms inoculated was estimated by plate count and therefore represents the number of viable bacterial clumps or chains.

[2] This, the smallest inoculum tested at the indicated time, gave 52 per cent mortality in a group of 25 mice, and has been taken as the approximate LD_{50} inoculum.

[3] Most of the animals actually receiving 1 to 2 bacterial chains or clumps died; the data therefore do not permit the estimation of the LD_{50} dose.

The several hundred fold increase in the number of organisms necessary to cause a fatal infection after exposure to penicillin agrees with the previous observation that 96 to 99 plus per cent of such penicillin-treated bacteria were killed by the mouse host in the six- to eight-hour period before they recovered sufficiently to resume multiplication. Because of the increased vulnerability of the penicillin-damaged bacteria to the host, a much larger number had to be injected in order to have an infectious inoculum still surviving by the time the organisms recovered and regained their normal resistance.

Qualitatively similar but quantitatively less striking and somewhat more variable results were obtained with the group A streptococcus. Two experiments with this organism are summarized in figure 3. When the penicillin-treated bacteria were inoculated intramuscularly, the recovery period in vivo was four to six hours instead of two to three hours, as in vitro. During that period the body was able to dispose of a significant proportion of the injected organisms, the percentage of surviving organisms varying in individual animals from 80 per cent to 2 per cent, with a median of 12 per cent after three

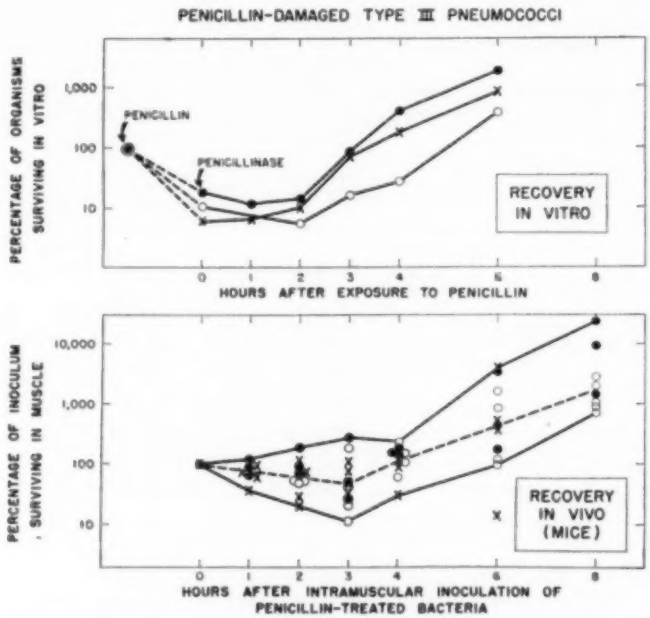

FIG. 4. The fate of penicillin-damaged Type III pneumococci in vitro and in vivo (mouse muscle). Summary of three experiments carried out at different times and differentiated in the figure by the symbols ○, ●, ×. (For details of the procedure used, cf. page 545 and the legend to figure 5.) In the bottom half of the figure, the lines have been drawn to indicate the range of variation.

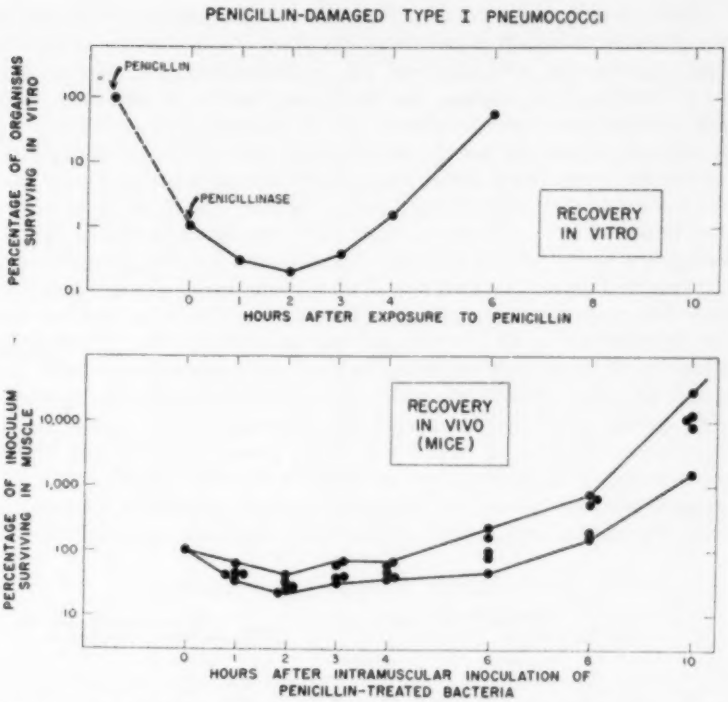
PENICILLIN-DAMAGED TYPE I PNEUMOCOCCI
PERCENTAGE OF ORGANISMS SURVIVING IN VITRO
PENICILLIN
PENICILLINASE
RECOVERY IN VITRO
HOURS AFTER EXPOSURE TO PENICILLIN
PERCENTAGE OF INOCULUM SURVIVING IN MUSCLE
RECOVERY IN VIVO (MICE)
HOURS AFTER INTRAMUSCULAR INOCULATION OF PENICILLIN-TREATED BACTERIA

FIG. 5. The fate of penicillin-damaged Type I pneumococci in vitro and in vivo (mouse muscle). A bacterial culture in the logarithmic phase of growth was diluted to contain 5×10^6 organisms per c.c. in blood broth containing sodium penicillin G in a final concentration of 0.1 microgram/c.c. After one and one-half hours at 37° C. (when 99 per cent of the organisms had already been killed) penicillinase was added and the mixture replaced at 37° to follow the recovery and remultiplication of the organisms in vitro (top curve in figure). Two minutes after the addition of penicillinase, 0.1 c.c. was inoculated intramuscularly into a number of mice. At the intervals indicated in the figure, the inoculated muscle was removed, emulsified in a Waring blendor, and the number of organisms determined by plate count. In the bottom half of the figure, as in figure 3 and the bottom half of figure 4, each point represents an individual animal sacrificed at the indicated time. The percentage of organisms surviving in the muscle has been referred to the average number recovered immediately after inoculation as 100. The lines have been drawn to indicate the range of variation in the experimental data.

hours. Corresponding to this increased vulnerability of the penicillin-damaged organisms to the host, it was necessary to inject a larger number in order to cause a fatal infection. As indicated in table 2, in one experiment the LD_{50} inoculum of viable penicillin-treated streptococci was 64, as contrasted with four for normal organisms. As the penicillin-damaged bacteria recovered their virulence returned to normal, the LD_{50} inoculum decreasing to 35 after two hours' recovery at 37° C., and back to one to two after four hours. In a second experiment, the LD_{50} inoculum was increased fifty-fold by similar exposure to penicillin, from five to 250 organisms.

Type I and type III pneumococci. The results obtained with pneumococci differed materially from those described above for the streptococci. Three experiments with the type III pneumococcus are summarized in figure 4 and figure 6. When this strain was exposed to penicillin in vitro there was the usual recovery period (in this instance, of two hours) before the damaged organisms had recovered sufficiently to resume multiplication. As with the streptococci, when such penicillin-treated bacteria were inoculated intramuscularly in mice they recovered more slowly than in vitro, the recovery period in vivo averaging four hours (cf. lower section of figure 4). During this entire period, however, the number of viable pneumococci decreased only slightly. In a total of 37 mice tested during the recovery period, the median proportion of organisms recovered one, two, three and four hours after inoculation was 75, 64, 45, and 110 per cent of those inoculated (cf. dashed line in lower half of figure 4). In approximately one-third of the animals the host exerted essentially no bactericidal action during that recovery period, and in the remainder, the proportion killed varied from 0 to 90 per cent. Under the conditions of the present experiments, although there was thus a suggestion that the mouse host could dispose of penicillin-damaged type III pneumococci somewhat more effectively than it could handle the normal and actively multiplying organisms, the difference was

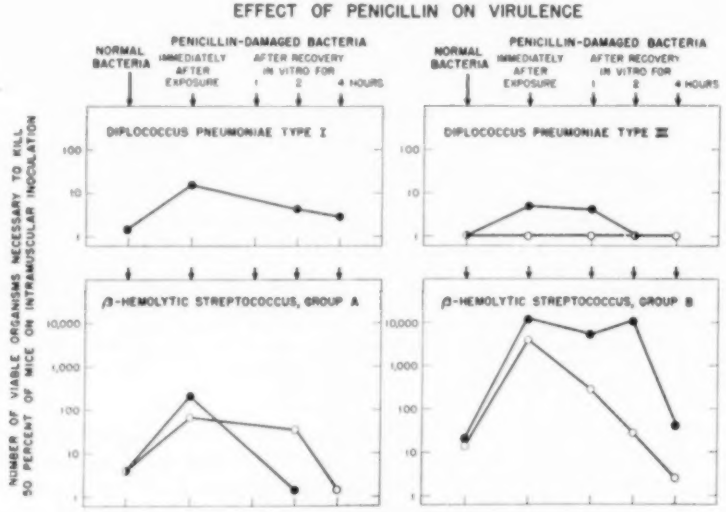

FIG. 6. The virulence of penicillin-damaged and recovering bacteria compared to that of untreated organisms simultaneously tested. Summary of a number of experiments with Group A and Group B β-hemolytic streptococci, Type I and Type III pneumococci. In all experiments the bacteria were exposed to penicillin at 0.1 microgram per c.c. The period of exposure was one and one-half hours, except for the case of the group A streptococcus (○——○, one hour) and the group B streptococcus (○——○, three hours).

TABLE III

The Effect of Varying Dosages of Sodium Penicillin G on an Intramuscular Depot of Type I Pneumococci in Mice

Dosage of Penicillin, mg./kg.	Percentage of Organisms Surviving[1] in Muscle[2] after						
	1	2	4	6	8	12	24 hrs.
200	23 13 11 8 5.2 2.7	0.81 0.5 0.45 0.44 0.44 0.36 0.29 0.27 0	0.81 0.5 0.44 0.37 0.3 <0.3 <0.3 0.06	0 0 0 0 0 0	0.06 0 0 0 0 0		0.13 0.06 0 0 0 0 0 0 0
Medians	9.5	0.44	0.33	0			0
3	26 16 13 13 9.7 8.9	9.3 8.7 7 6.6 4.4 3.8	16 16 14 2.5 1.6 0.87	374 268 163 16 6.2	140 125 90 54 38 24 4.7	1,280 470 410 310 120 92 10.7	82,600 77,000 46,800 2,000 1,160 27
Medians	13	6.8	5.9	163	54	310	9,660
0.6	35 33 29 23 13 10	68 43 40 36 27 16	690 390 320 87 39 12	2,470 940 870 760 750 200	1,420 660 370 200 175 115 85	5,000± 5,000± 4,080 1,400 700 210 110	180,000 51,200 16,000 14,700 8,300 6,000 9.3
Medians	26	38	167	813	200	1,400	14,700
0.15	87 70 66 62 40 32	245 175 140 120 80 75	1,630 1,400 1,000 630 175		4,900 1,750 400	23,800 14,700 1,500	864,000 20,000 5,400
Medians	64	130	1,000				
0	190 180 167 161 120 117 92 90 80	420 340 270 250 230 200 180 164 160	6,290 4,020 1,600 1,400 940 870 860 410		11,900 8,200 5,400 3,500 3,500 2,700	75,000 61,600 50,800 50,600 6,200	1,561,500 306,000 584,600 146,100 144,000 51,200 35,400
Medians	120	230	1,140		4,350	50,800	146,100

[1] The bacterial counts have been expressed as percentages, referred to the number of organisms recovered from muscles immediately after inoculation as 100. In 19 control mice, the number so recovered varied between 52 and 346 per cent of the number growing out from the bacterial suspension used for inoculation (cf. page 545).

[2] During the period that the bacteria were decreasing in number under the impact of penicillin, and often for many hours after they had begun to re-multiply in the inoculated muscle, no organisms could be recovered from the blood, liver, spleen or lung.

[3] Interpolations were done on a logarithmic scale.

not striking, and in many of the animals there was no evidence of an enhanced susceptibility.

This resistance of penicillin-treated type III pneumococci to the defenses of the mouse host was confirmed when serial dilutions of such penicillin-treated suspensions were inoculated intramuscularly as a test of virulence (cf. table 2 and figure 6). With normal pneumococci, in two experiments carried out at different times, one organism (i.e., one short bacterial chain) killed more than half the animals. Immediately after exposure to penicillin for one and one-half hours, and after 82 and 94 per cent of the organisms had already been killed, the LD_{50} inoculum was < two organisms in one experiment, and approximately six in a second experiment. Even when confronted with damaged and non-multiplying bacteria, in a three-hour period the mouse host could therefore dispose of only a small and sometimes negligible number of organisms.

TABLE IV

The Effect of Varying Dosages of Sodium Penicillin G on an Intramuscular Depot of Group B Streptococci in Mice

Dosage of Penicillin, mg./kg.	Percentage of Organisms Surviving[1] in Muscle[2] after									
	1/2	1	2	3	4	6	8	12	24	48
200	75 45	35 34 30 16	30 27 19 11	3.1	15 15 5.3 1.6	5.3 3.1 2.9 2.2	1.9 1.6 0.6 0.56	0.83 0.6 0.58 0.3 0.25 0.25	0.5 0.24 0.23 0.12 0.03 0 0 0	0 0 0 0
Medians		32	23		8.9	3.0	1.0	0.42	0.06	0
3	41	45 26 26 12	24 22 11 7.4	16 12 11 4.3	19 9.5 4.1 2.5	21 6 5.4 2.9	100 18 14 7.9 3	18 9.5 1.4 1.3 0.56	17 1.4 0.66 0.37 0.33 0.24 0.13	0 0 0 0 0
Medians		26	16	12	6.2	5.7	14	1.4	0.37	0
0.6		70 63 57 51	26 26 18 12		13 10 6 2.5	8 7 3.8	30 11 4.0 2.8 2.3 1.5 1.5	1,630 73 23 4.2 3.6 0	1,450 420 220 35 0.33 0.16 0 0 0	22,000 2,400 0 0 0
Medians		60	22		8		2.8	9.8	0.33	0

TABLE IV—*Continued*

Dosage of Penicillin, mg./kg.	Percentage of Organisms Surviving[1] in Muscle[2] after									
	1/2	1	2	3	4	6	8	12	24	48
0.15	215 175 154	270 190 118 90 86	370 350 118 82	N.G.	495 425 160 100	3,600 150	2,800 1,860 740 285 150 23	8,930 4,200 4,000 1,300 540 31	86,000 34,800 20,670 4,400 155 7.6	700,000 3,200 3,200 1,700 0
Medians		118	203		261		460	2,280	9,540	3,200
0.075		160 92 75	290 200 82	830 218	290 268 260	6,790 1,920	8,200 3,930 35	41,000 33,570 1,223	19,280 10,000	
0		415 295 295 275 220 217 190 186	790 620 610 565 560 190 93		3,980 2,710 1,345 1,170 1,000 710 510 505	5,905 2,950 880 445 242 105		7,930,000 86,900 23,000 6,740 5,570 2,090 348 48	283,000 14,200 13,700 360 48	
Medians		245	565		1,080	626		6,100		

[1] The bacterial counts have been expressed as percentages, referred to the number of organisms recovered from muscles immediately after inoculation as 100. In 17 control mice, the number so recovered varied between 82 and 353 per cent of the number growing out from the bacterial suspension used for inoculation (cf. page 545).

[2] During the period that the bacteria were decreasing in number under the impact of penicillin, and often for many hours after they had begun to re-multiply in the inoculated muscle, no organisms could be recovered from the blood, liver, spleen or lung.

[3] Interpolations were done on a logarithmic scale.

Similar results were obtained with the type I pneumococcus. The penicillin-damaged bacteria were not strikingly affected by the host (figure 5), and were only slightly less virulent than the normal organisms (figure 6). After preliminary exposure to penicillin for one and one-half hours in vitro, when 99 per cent of the organisms had already been killed, and the survivors did not recover for three hours, the LD_{50} inoculum on intramuscular inoculation was 15 bacteria; the LD_{50} inoculum of normal organisms simultaneously tested was approximately one to two (cf. table 2 and figure 6).

In summary, judged both by the death of the organisms on intramuscular inoculation and by the larger number necessary to cause a fatal infection, penicillin-damaged streptococci of groups A and B were considerably more susceptible to the host defense mechanisms than normal bacteria. In contrast, the virulence of similarly treated pneumococci of types I and III was only moderately diminished, and on intramuscular inoculation a large proportion of the organisms remained unaffected by the host until they had recovered sufficiently to resume multiplication.

II. An Analysis of the Bactericidal Action of Penicillin in Vivo

The experimental data of the foregoing section, and the conclusions drawn from those data, were confirmed by a direct study of the bactericidal action of penicillin in vivo. White mice were inoculated intramuscularly with each of the four strains here studied, and immediately treated intramuscularly in the opposite leg with sodium penicillin G in varying dosage (cf. page 545). At each dosage level, groups of mice were then sacrificed at intervals in order to determine the number of organisms still surviving. The results with the type I pneumococcus and the group B streptococcus are given in detail in tables 3 and 4, and all the experiments are summarized in figures 7 to 10. Each point in those figures is the median number of organisms surviving in each experimental group of four to 12 mice tested.

A. *The Direct Bactericidal Action of Penicillin.* The dotted portion of the curves in figures 7 to 10 represents the average time for which the serum penicillin remained in excess of the concentration necessary to provide the bactericidal level at the focus of infection.* [5, 8] With each of the four organisms here studied, the initial rate at which the organisms were killed was independent of the dosage, provided only that it was enough to supply the effective concentration at the focus of infection.† The organisms died no faster at a dosage of 200 mg./kg. than they did at 20, 3 or even at 0.6 mg./kg. The large doses merely provided effective concentrations for a longer time (cf. the dotted portions of 200, 20, 3, and 0.6 mg./kg. curves in figures 7 to 10); while the small doses which failed to kill either did not provide an effective concentration or provided it for a short and inadequate period. These data therefore do not support the thesis that large doses of sodium penicillin, providing concentrations far in excess of those necessary to kill the bacteria at a maximal rate,‡ have a therapeutic effect greater than that of repeated smaller doses which in the aggregate

* It has been shown in a preceding paper [8] that in order to kill the strains here used of group A and group B streptococci, and of type I and type III pneumococci, all inoculated intramuscularly in mice, the serum concentrations must be in excess of 0.012, 0.08, 0.08 and 0.08 micrograms/c.c., respectively. These serum concentrations probably provide the barely bactericidal level in the muscle, and somewhat higher concentrations (two- to threefold) would be necessary to kill the organisms at the maximal rate. However, because of the rapid rate at which sodium penicillin disappears from the serum of mice,[5, 8, 9] the time for which it remains at the barely bactericidal level after a large dose is essentially the same as the time for which it remains at the maximally effective level.

It was further shown in a previous paper [8] that penicillin does not remain at effective concentrations in the muscles of rabbits or mice for a significant period after it has fallen below those levels in the serum. If animals are given a single large injection of aqueous penicillin, and at varying intervals thereafter are inoculated with a small number of virulent bacteria, the infection is aborted only if the organisms are inoculated 30 to 60 minutes *before* penicillin in measurable concentrations disappears from the serum. The failure of penicillin to persist in the muscle is further shown by the fact that the rapid phase of bactericidal action usually stops abruptly as soon as the serum penicillin falls below the effective level.

† Unlike sodium penicillin G in aqueous solution as here used, with a suspension of procaine penicillin in oil with aluminum monostearate one can vary the dosage so as to maintain the serum concentration in a range which is bactericidal, but at which the organisms are killed at less than the maximal rate. In that narrow threshold range, the rate at which the bacteria die in vivo becomes a function of dosage.

‡ Refers to footnote marked * on preceding page.

provide the maximally effective concentration at the focus of infection for the same total period of time.[5] On the other hand, a large dose may promote the penetration of penicillin into walled-off foci of infection which are only slowly equilibrated with the tissue fluids, and into which penicillin might not diffuse in adequate concentration after a small dose which provides a low "head of pressure" for a relatively brief period. Of importance also is the fact that after a longer exposure to penicillin it may take the surviving bacteria a longer time to recover from the toxic effects of the drug and to resume multiplication.

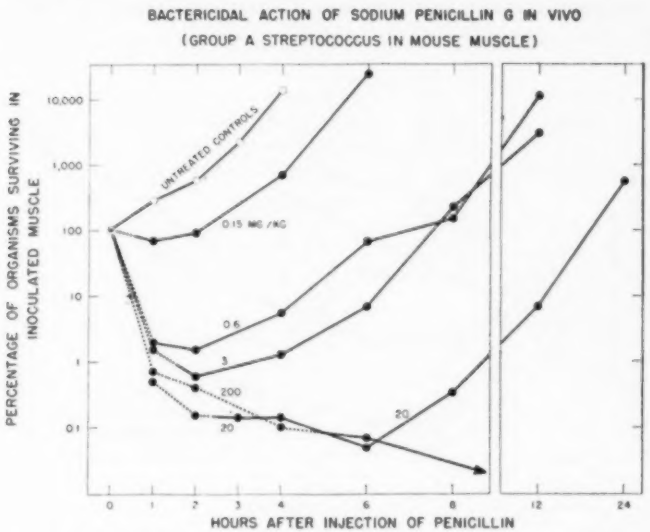

FIG. 7. The bactericidal action of penicillin on intramuscular foci of Group A β-hemolytic streptococci in white mice (after data of table 5). The procedure used in the experiments of figures 7 to 10 has been described on page 545. In this figure, as in the following figures 8 to 10, each point represents the median value in groups of 4 to 12 mice sacrificed at the indicated time. The actual experimental data are given in detail for two bacterial species in tables 3 and 4.

Rate of bactericidal action in vivo and in vitro. In three of the four bacteria species here studied, the rate of bactericidal action in vitro and in vivo were essentially the same. In vitro, at maximally effective concentrations, penicillin killed 99.9 per cent of group A streptococci, type I pneumococci and type III pneumococci in 1.5–3, 3–4 and 3–4 hours, respectively. The average times necessary to kill 99.9 per cent of the same organisms in vivo (figures 7, 8 and 9) were 4, 5, and 3 hours, respectively. With these three species, there was thus no indication that the host had either accelerated or significantly retarded the direct bactericidal action of penicillin.

Quite different results, however, were obtained with the group B streptococcus. This organism is one of a large group of bacteria which in vitro shows a zonal susceptibility to penicillin:[10] (*a*) low concentrations, less than 0.016 microgram per c.c. have no effect on this strain; (*b*) there follows a narrow range of concentrations within which the rate of bactericidal action increases with concentration, to reach a maximum at 0.064–0.128 microgram/c.c.; (*c*) at concentrations in excess of this optimal level, the rate of bactericidal action *decreases* with increasing concentration of drug. Thus, at 256 μg./c.c. it required 23 hours to kill 99.9 per cent of the organisms, as compared with six to seven hours at 0.064 μg./c.c.; and after six hours at 37° the proportion of survivors was 15 per cent instead of 0.06 to 0.08 per cent.

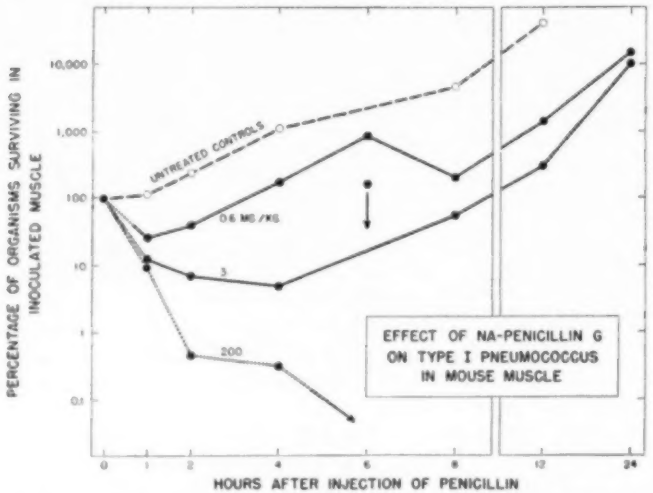

FIG. 8. The bactericidal action of penicillin on intramuscular foci of Type I pneumococci, after data of table 3 (cf. legend to figure 7).

The dosages of 200 mg./kg. and 3 mg./kg. initially provided concentrations within this last zonal range of retarded bactericidal activity. Correspondingly, at those dosages, even during the initial period of penicillin action (indicated by the dotted portion of the curves), the organism was killed far more slowly in vivo than were the other three, non-zonal species. This is evident on comparing figure 10 with figures 7 to 9. Four hours after the injection of 200 mg./kg., the median percentage of organisms surviving was 10, instead of 0.03 to 0.3, as with the other three species. This rate of death in vivo approximates that at which the organisms are killed by concentrations in excess of 1 microgram per c.c. in vitro, and is far less than the rate at which they are killed by, for example, 0.1 μg./c.c.[11]

Further, the death of these organisms in vivo is not the result of penicillin action alone, but includes the pronounced bactericidal effect of the host defenses on penicillin-damaged organisms (cf. page 547 and figure 1); and the direct bactericidal action of penicillin as such is probably even slower than the foregoing figures would indicate.

These considerations suggest that the paradoxically reduced rate of bactericidal action noted with some bacterial species at high concentrations of penicillin is also observed in vivo. In the therapeutic use of penicillin, consideration must therefore be given to the fact that with certain zonal strains the concentrations provided by sodium penicillin in ordinary therapeutic doses may kill the organism at a greatly reduced rate, and that in order to effect cure treatment must then be continued for a longer aggregate period than would otherwise be necessary.

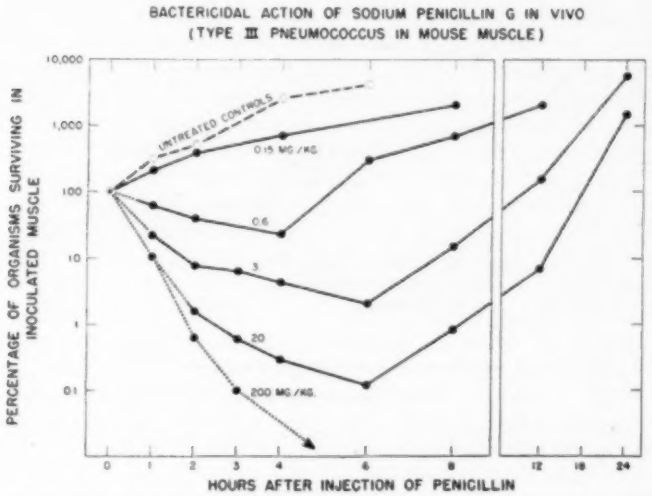

FIG. 9. The bactericidal action of penicillin on intramuscular foci of Type III pneumococci (cf. legend to figure 7).

B. *The Post-Penicillin Recovery Period in Vivo.* As soon as the concentration of penicillin in the serum fell below that necessary to provide a bactericidal concentration at the focus of infection, the direct action of the drug stopped. However, the surviving and penicillin-damaged bacteria did not immediately resume multiplication. As had been observed in vitro,[1, 2, 3, 17] and as was indicated by the experiments of the preceding section, there followed instead a period during which the surviving and damaged bacteria slowly recovered from the toxic effects of the drug, without multiplying during that recovery period.

1. *Duration of recovery period.** In vitro, the four strains here studied had a maximum recovery time of two to three hours.[3] † When penicillin-damaged bacteria were inoculated intramuscularly, the recovery period in vivo was regularly longer than the recovery period in vitro (cf. page 551). In the present experiments also, when bacteria were exposed to penicillin in vivo, the time required for their recovery and remultiplication at large doses of penicillin was usually longer than the corresponding recovery time in vitro, averaging 3, 3–5, 5 and > 20 hours for the group A streptococcus, type I and type III pneumococci, and the group B streptococcus here studied (cf. figures 7 to 10, tables 3 and 4).

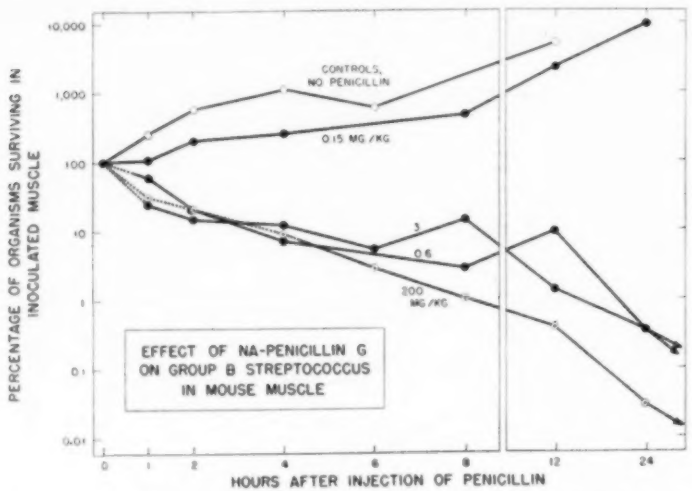

FIG. 10. The bactericidal action of penicillin on intramuscular foci of Group B β-hemolytic streptococci, after data of table 4 (cf. legend to figure 7).

The time for which bacteria must be exposed to penicillin in order to produce this sublethal damage, and the concentrations of drug necessary, are important practical considerations. In vitro, the most rapidly damaging concentration has been shown to be the same as that which kills the organ-

* The foregoing discussion on the duration of the bactericidal action of penicillin, and the present section on the duration of the following recovery period, are based on the median values in groups of four to 12 mice. In individual animals there was considerable variation with respect to both time periods. In consequence, although the number of surviving bacteria in individual mice differed only slightly during the initial phase of bactericidal action, those differences became significant at the beginning of the recovery period (reflecting minor differences in the duration of penicillin action), and became increasingly marked toward the end of the recovery period, when the organisms had begun to remultiply in some animals while they were still recovering in others. This increasing individual variability is evident in the data of tables 3 and 4, and in figures 1, 2, 3 and 4.

† The significantly longer recovery period observed with the group B streptococcus after exposure to penicillin for 24 hours[3] is not germane to the present discussion.

isms at the maximal rate.[3] Concentrations in excess of that level usually do not further accelerate the damage to the organisms; and at lower concentrations the damage to the organisms, measured by the duration of the following recovery periods, proceeds more slowly.

The same relationships were found to obtain when penicillin acted on bacteria in vivo. Thus, for the type I and type III pneumococci here studied, the maximum damage to the organism (maximum recovery period) was effected in vitro by exposures to concentrations > 0.064 μg./c.c. for one-half to one hour.[3] The serum level providing that concentration at an intramuscular focus in mice may be estimated to be on the order of 0.2–0.3 μg./c.c. (cf.[8]). Dosages of 20, 3, 0.6 and 0.15 mg./kg. supply that level for periods of approximately 1.4, 0.7, 0.4 and 0 hours, respectively; and, after exposure to penicillin for those periods, type III pneumococci recovered and resumed multiplication in half the animals in 4, 5, 3.5 and 0 hours, respectively. The maximum damage to the organisms short of actual loss of viability was therefore effected by exposure to the maximally effective concentration for approximately 0.4–0.7 hours; and longer exposure, or exposure to much higher concentrations, did not further prolong the recovery period.

With the group A streptococcus also, which in vitro gives a maximal recovery period after exposure to 0.064 μg./c.c. for 30 minutes, dosages of 20, 3 and 0.6 mg./kg., providing serum concentrations in excess of 0.1 μg./c.c. for 1.6, 0.9 and 0.5 hours, respectively, were followed by average recovery periods of approximately 4, 2, and 2 hours, respectively; and a dosage of 0.15 mg./kg., which provides a serum concentration in excess of 0.1 μg./c.c. for less than 10 minutes,[8] and more slowly bactericidal concentrations (in excess of 0.012 μg./c.c.[8]) for 40 minutes, was followed by a recovery period of approximately one and one-half hours (figure 7).

In summary, with these three organisms, it required essentially the same exposure to penicillin in vivo as in vitro in order to cause the sublethal damage reflected by a delayed multiplication after the disappearance of the drug. At the most rapidly bactericidal concentration, the maximum damage (longest recovery period) was effected within approximately one hour. There was no evidence in the present experiments that higher concentrations of penicillin, or longer exposure, further prolonged the recovery period in vivo. However, this important point requires further study.

With the group B streptococcus (cf. table 4 and figure 10), the recovery phenomenon in vivo differed materially from that observed in vitro, or from that of the other three species here studied, and in two important respects. With the other species the recovery period in vivo was only slightly longer than that in vitro and ranged between three and five hours, while with this organism the recovery period in vivo was more than 24 to 48 hours. After a dosage as low as 0.6 μg./kg., which provided an effective concentration of penicillin for approximately 30 minutes, the bacteria did not resume multiplication for 24 hours, and in only two of five mice tested had the organisms remultiplied even after 48 hours. With this organism, also, a striking aspect

of the recovery period, over and above its unusual length, was the continuing slow death of the penicillin-damaged organisms over this entire period, for 24 to 48 hours after the penicillin itself had fallen to ineffective levels. This aspect of the recovery period is discussed in the following paragraph.

2. *The continuing death of penicillin-damaged bacteria during the recovery period, after the disappearance of penicillin.* When group B streptococci were exposed to penicillin in vitro and then inoculated, the organisms were found to have been rendered highly susceptible to the host defenses (cf. page 547). Similarly, when normal group B streptococci bacteria were inoculated intramuscularly, and the effects of penicillin were followed in vivo, the bactericidal effect of penicillin continued long after the drug itself had disappeared. The penicillin-damaged organisms had been rendered vulnerable to the mouse host, and large proportions of the surviving bacteria were rendered non-viable in the course of the recovery period, after the disappearance of the drug. At doses of 200, 3, and 0.6 mg./kg., the median percentage of organisms killed during the period of direct penicillin action was only 90, 75, and 25 per cent, respectively. At the two larger doses, all the surviving organisms were disposed of by the host in the following 24 to 48 hours. Even at the 0.6 mg./kg. dose, which provided effective concentrations of penicillin for only 30 minutes (when 75 per cent of the bacteria were still viable), the organisms continued to die for periods which in individual mice varied from eight to 48 hours (cf. table 8). The continuing action of the host on the penicillin-damaged bacteria was quantitatively far more important than the direct action of the drug itself.

With the other organisms here studied, however, the contribution of the host to the bactericidal action of penicillin under the conditions of the present experiment was comparatively minor. When the drug fell to ineffective levels (end of dotted curves in figures 8 to 10), the rate of death was sharply reduced. Although, confirming the results obtained by Jawetz [6] in a streptococcal infection in mice, the number of viable organisms usually continued to decrease in the following recovery period (cf. curves 200 and 3 mg./kg. in figure 8; 3 and 0.6 mg./kg. in figure 9), the effect was quantitatively small in relation to that produced by the preceding direct bactericidal action of the drug.

C. *Re-multiplication of the Surviving Organisms After Their Recovery from the Toxic Effects of Penicillin.* Eventually, when the surviving bacteria had fully recovered from the toxic effects of penicillin, they resumed multiplication at the same rate as normal organisms similarly inoculated. This is shown on the right-hand side of figures 7 to 10. Thereafter, the longer the time interval the greater was the degree to which that remultiplication counteracted the bactericidal effect of the preceding injection of penicillin. The combined duration of the recovery period and the time it then takes the surviving bacteria to remultiply up to their original number represents the maximum penicillin-free interval between injections which is consistent with a net therapeutic effect. It is apparent that this maximum

permissible penicillin-free interval will vary with the rate of recovery of the particular organism, its rate of growth in vivo, and will depend also on the number of organisms surviving. If only a small proportion had been killed by the previous treatment, remultiplication for as little as one to two hours might effectively counteract the effect of the preceding injection (cf. 0.15 mg./kg. curve in figures 7 and 10; 0.6 mg./kg. curve in figures 8 and 10). On the other hand, if, for example, 99.99 per cent had been killed, the surviving and recovered bacteria might have to remultiply for four to eight hours

TABLE V

The Effect of the Dosage of Sodium Penicillin G in Mice on the Duration of the Following Recovery Period and the Maximum Safe Interval between Injections
(After data of tables 3 and 4 and figures 7 to 10)

Bacterial Species	Dosage of Penicillin, mg./kg. (Intramuscular)	(1) Average Time for Which Serum Penicillin Remained at Effective Levels,[1] hours	(2) Median Duration of the Following Recovery Period, hours[2]	(3) Total Interval between Injections Consistent with No Remultiplication of Survivors[3] (1) + (2)	(4) Maximum "Safe" Period of Remultiplication, hours[3]	(5) Maximum Interval between Injections Consistent with Net Therapeutic Effect[4] in Half the Animals (3) + (4)
β-Hemolytic streptococcus, group A	200	5	(cured)	?	(cured)	?
	20	2.5	3.5	6	12–14	18–20
	3	1.4	2–3	2–3	3–4	7–8
	0.6	1.0	1.5–2	2	3–4	7
	0.15	0.6	1½		0	2
β-Hemolytic streptococcus, group B	200	4.5	>40	>40	(cured)	>48
	3	0.9	>40	>40	(cured)	>48
	0.6	0.6	>40	>40	(cured)	>48
	0.15	0.2	0.8 ?	< 1	0	< 1
Diplococcus pneumoniae, Type I	200	4.5	(cured)	?	(cured)	?
	3	0.9	3–4	4–5	2–5	6–10
	0.6	0.6	1±	1–2	1–2	3–4
	0.15	0.2	0	<0.5	0	<0.5
Diplococcus pneumoniae, Type III	200	4.5	(cured)	?	(cured)	?
	20	1.9	4	6	12	18
	3	0.9	3	4–6	10	10–12
	0.6	0.6	3.5	4	1	5
	0.15	0.2	0	<0.5	0	<0.5

[1] I.e., at levels sufficient to provide a bactericidal concentration at the intramuscular focus. Those serum concentrations have been estimated at 0.012 microgram per c.c. for the group A streptococcus, and 0.08 microgram per c.c. for the other 3 organisms here studied.[5] The times given in this column are thus the times for which the penicillin remained at the barely bactericidal rather than the maximally effective level. However, because of the rapid rate at which penicillin disappears from the serum, at dosages of 0.6–200 mg./kg. the two time periods would differ to an insignificant degree.

[2] These are averages based on the median values (cf. tables 3 and 4); as there shown, individual mice varied considerably with respect to the time at which remultiplication began.

[3] The time for which the recovered bacteria could remultiply without exceeding the original inoculum. These times are based on the median values plotted in figures 7 to 10, and therefore apply to only half the mice. In the other half, the recovered organisms would already have resumed multiplication.

[4] I.e., permitting remultiplication of survivors, but not up to their original number. Half the animals would die on this regimen of treatment, and half would eventually be cured.

before the total number returned to its original level (cf. 3 mg./kg. and 20 mg./kg. curves in figures 7 to 10). Small doses would therefore have to be repeated often in order to effect cure, while larger doses could be given at intervals of four, eight, 12 or even 24 hours. These relationships are summarized in table 5 for each of the four organisms here studied, at each of five dosage levels. The time periods there given are based on the curves of figures 7 to 10. (It should be emphasized that the points in those curves are median values, and that in individual mice there was considerable variation with respect to the duration of penicillin action, the extent of the following recovery period and, ultimately, the rate of remultiplication (cf. footnote,* page 562).

In man, satisfactory results have been obtained in the treatment of pneumococcal [11, 12] and other infections [13, 14] with large doses of aqueous penicillin given once or twice daily. Smaller doses would have permitted recovery and remultiplication of the surviving organisms, while at the larger and eventually curative doses there may be some remultiplication of the surviving and recovered organisms, but not enough to counteract the therapeutic effect of the preceding injection.

Discussion

The Participation of the Host in the Therapeutic Action of Penicillin. The bactericidal action of penicillin in vivo has here been studied with four bacterial species inoculated intramuscularly into mice. In three of the four (group A streptococcus, type I and type III pneumococcus) under the conditions of the present experiments, the direct bactericidal action of the drug was by far the most important factor in its therapeutic action. The bacteria died at a rapid rate only so long as the drug remained at effective levels, and that rate approximated that at which the organisms were killed by penicillin in vitro. When the concentration of drug had fallen below the effective level, the rapid phase of bactericidal action ceased. The then surviving and penicillin-damaged organisms did not resume multiplication for a number of hours, during which time they were presumably recovering from the toxic effects of the drug. This recovery period in vivo parallels the similar recovery of penicillin-damaged bacteria in vitro.[1, 2, 3, 17] Its duration as affected by the duration of the preceding exposure to penicillin has been discussed on pages 562 and 563.

The recovering organisms were somewhat more susceptible to the host than normal bacteria. This was reflected by a significant if irregular decrease in the number of survivors during the recovery period, after penicillin was no longer present in effective concentrations, and agrees with a similar observation by Jawetz in a group A streptococcal infection in mice. If the group A streptococci were exposed to penicillin in vitro and then inoculated, there was a similar decrease in the number of viable organisms at the site of inoculation, until the bacteria had recovered sufficiently to resume multiplication. Corresponding to this increased vulnerability, the minimal in-

fectious inoculum of the penicillin-damaged organisms was 20 to 40 times greater than that of normal bacteria.

In the case of the pneumococci, however, the host had but little effect even on the penicillin-damaged organisms, and the minimal infectious inoculum differed only slightly and irregularly from that of the normal bacteria.

The group B streptococcus differed markedly from the other three species here studied with respect to the degree of host participation in the therapeutic action of penicillin. Exposure to penicillin in vitro or in vivo strikingly enhanced the susceptibility of this organism to the host, and on the order of 99 per cent of such penicillin-damaged bacteria were killed before they recovered sufficiently to resume multiplication. Correspondingly, the minimal lethal inoculum of such penicillin-treated bacteria was several hundred times greater than that of normal, untreated streptococci. Not only were the penicillin damaged organisms more vulnerable to the host, but their recovery period in vivo was extraordinarily prolonged. After a single small injection of penicillin, which provided effective concentrations of penicillin for only 30 minutes, the bacteria did not resume multiplication for 24 to 48 hours. During this entire period, the number of viable organisms steadily decreased at a rate comparable to the rate of bactericidal action of the drug itself. With this organism, therefore, the continuing death of the penicillin-damaged bacteria, after the drug itself was no longer present in effective concentration, was quantitatively far more important than the direct bactericidal action of the drug as such.

The fact that the bactericidal action continued uninterruptedly as the penicillin fell to ineffective levels and the host mechanisms alone continued the bactericidal process, and the further observation that when penicillin-damaged bacteria were inoculated intramuscularly, the number of viable bacteria began to decrease immediately (cf. figure 1), both suggest that humoral rather than cellular mechanisms may be involved. The death of these penicillin-damaged streptococci in the body fluids may possibly be related to the fact that bacteria similarly damaged by penicillin in vitro also become non-viable if transferred to an insufficiently enriched fluid medium. In both cases, the environment may be deficient in a metabolite essential for the recovery of the damaged bacteria.

The fact that with three of the four organisms here studied (type I and type III pneumococci, and group A streptococci), the contribution of the mouse host to the therapeutic action of penicillin was quantitatively unimportant in relation to the direct bactericidal action of the drug should perhaps not be over-emphasized. The present experiments did not involve actual infections, since the drug was injected immediately after the bacteria and before an inflammatory reaction had developed at the site of inoculation. Had there already been a local cellular response, those phagocytic cells might have been able to dispose of bacteria damaged by the previous exposure to penicillin, and the participation of the host might have been more

pronounced than was here the case. It is nevertheless pertinent to note that as few as one to six such penicillin-damaged pneumococci were capable of initiating a fatal infection. This indicates that such defenses as the host could mobilize over a three-hour period (when the organisms had recovered sufficiently to resume multiplication) were unable to dispose of even this small inoculum. An additional factor which is not considered in the acute experiments here discussed is the possible contribution of specific antibodies to the therapeutic action of penicillin. The organisms caused a rapidly fatal infection, and the animals died before they could develop sufficient humoral antibody to affect its course. The degree to which such antibodies may modify or supplement the direct bactericidal action of penicillin remains to be determined. In any case, it seems clear from the present experiments that with some bacterial species, the drug as such need not effect total sterilization in order to effect cure, in that the host defenses may be able to dispose of residual penicillin-damaged organisms before they recover sufficiently to resume multiplication.

Implications of Present Observations With Respect to the Schedule of Penicillin Administration. The present experiments help resolve an apparent contradiction with respect to the mechanism of the therapeutic action of penicillin in vivo. The major importance of its direct bactericidal action is indicated by the fact that the minimum concentration which is effective against a given organism in vivo is of the same order of magnitude as that which is bactericidal in vitro.[8] Further, although the curative dose of penicillin in a given experimental infection may vary markedly according to the schedule of its administration, those widely disparate curative doses usually provide the bactericidal concentration for the same aggregate period of time.[5] These data suggest that the concentration of penicillin in the tissues and the total time for which it remains at effective levels are of critical significance.

In apparent contradiction to this thesis are the clear-cut findings in both animals [6, 7, 15, 16] and man [11, 12, 13, 14, 17] that treatment with penicillin need not be continuous, but that it can be given intermittently, with long periods during which the concentration in the serum (and presumably in the tissue fluids) is far below the level bactericidal for the particular organism. Jawetz [6] had previously shown that in a streptococcal infection of mice the bacteria continued to disappear from the tissues for hours after penicillin itself had fallen to ineffective levels; and it was shown in a previous study from this laboratory that when penicillin was given on an intermittent schedule of treatment, in some infections the drug then had to be provided at effective levels for an even shorter period than when the effective level was continuously maintained.[5] (Only when the penicillin-free interval between injections was unduly prolonged did the bacteria remultiply sufficiently to counteract in part or in whole the therapeutic effect of the preceding injection.)

As suggested in a previous paper,[16] and as here discussed in detail, the probable explanation of this contradiction lies in the properties of bacteria which have been exposed to bactericidal concentrations of penicillin. In addition to the fact that the organisms do not resume multiplication for a number of hours after penicillin has disappeared, in some infections these recovering organisms are significantly more susceptible to the defense mechanisms of the host, and continue to die as an aftermath of penicillin action long after the drug itself has fallen to ineffective levels. The duration of this recovery period in vivo has been here shown to vary widely among different bacterial species, as does the vulnerability to the host of the surviving and penicillin-damaged organisms.

Although penicillin can therefore be administered on an intermittent schedule without necessarily maintaining its concentration at an effective level, it is a reasonable presumption that bacteria would die more rapidly under the combined impact of penicillin and the host defenses than under the latter alone, and that a maintained bactericidal level would therefore be more rapidly effective than a schedule of treatment supplying that bactericidal concentration only intermittently. With three of the four organisms here studied, this proved to be the case, and the rate of bactericidal action fell sharply as soon as the penicillin fell to ineffective levels. Only with the group B streptococcus, in which the action of the mouse host on the penicillin-damaged bacteria outweighs the direct bactericidal action of the drug, was the rate of death of the bacteria apparently unrelated to the continuing presence of penicillin in effective concentration.

Summary

1. Under the conditions of the present experiments, the rate at which streptococci and pneumococci were killed by penicillin in vivo approximated their rate of death in vitro. A zone-type organism which in vitro was killed more slowly at high concentrations of the drug than at lower concentrations was killed in mice at the slow zonal rate.

2. With three of the four species studied (type I and type III pneumococci, and a group A streptococcus), the rapid bactericidal action stopped abruptly as soon as the serum penicillin fell to ineffective levels. However, the surviving organisms did not resume multiplication for a number of hours thereafter. This recovery period in vivo was usually longer than that observed in vitro, and with these three strains varied from two to five hours. The maximum damage to the organisms (i.e., maximum recovery period) was accomplished by exposure to the effective concentration of penicillin for a period of approximately one hour; and longer exposure, or exposure to much higher concentrations, did not significantly prolong the time required for the bacteria to recover and resume multiplication.

During the recovery period, a small but significant proportion of the surviving organisms was disposed of by the host in the absence of penicillin.

This increased vulnerability of the penicillin-damaged organisms was also observed when bacteria previously exposed to penicillin in vitro were inoculated intramuscularly in mice.

3. With the fourth species (a group B streptococcus), the continuing action of the host on the penicillin-damaged bacteria was quantitatively far more important than the direct bactericidal action of the drug. After a dose which provided effective levels of penicillin for only one-half to one hour, the bacteria continued to die for periods of 24 to 48 hours, and at a rate comparable to that observed during the initial period of drug action. The strikingly enhanced susceptibility of these penicillin-damaged organisms to the host was confirmed when bacteria were exposed to penicillin in vitro and then inoculated. The minimal infectious dose was then several hundred times greater than normal, and 98 to 99 per cent of the organisms were rendered non-viable before they had recovered sufficiently to regain their normal resistance.

4. The implications of these observations with respect to the therapeutic use of penic...in are discussed in the text.

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HEART DISEASE: ITS MEDICAL ASPECTS*

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It is not surprising that the medical profession and the entire country are intensely concerned with the problem of heart disease. From a public health point of view it outranks all others in importance. As far as the medical profession is concerned, heart disease is no longer confined to the field of internal medicine. The surgeon has now taken on a major responsibility in the treatment of an increasing number of types of heart disease. Specialists in many other fields often find that the heart plays an important rôle in the diseases under their care. The dermatologist may be treating a case of lupus erythematosus or scleroderma, but knows that the heart may become involved in these conditions. The orthopedic surgeon may be struggling with a stubborn case of kyphoscoliosis and knows, or should know, that chronic cor pulmonale or cardiorespiratory failure is a common terminal eventuality. He also should realize that it is vital to prevent this final complication by early correction of the thoracic deformity, because treatment after it develops is unsatisfactory. The industrial physician is aware that the common end-result of berylliosis and silicosis is chronic right heart failure. One may continue at great length to show that the heart suffers burdens either directly or indirectly from a wide variety of diseases, and that all physicians at one time or another are concerned with its problems.

It is the purpose of this discussion to direct attention to the subject of heart disease as it concerns the internist or general practitioner. This will include those problems that are primarily cardiac in origin, as well as the more heterogeneous group in which the cardiac aspects are secondary or complications, often very vital, to other underlying diseases. Obviously, if there is a surgical aspect to the case, a proper diagnosis will first be necessary at the hands of an internist, as the patient is not likely to come to the surgeon except on the advice of a physician.

Prevention: Before considering the important problems of diagnosis and treatment, it is appropriate to spend a moment on prevention. Much is said concerning the prevention of heart disease, although very little is known. That does not mean we should not take advantage of the little that is available. It is now generally accepted that German measles occurring during the first three months of pregnancy often produce congenital malformations in the fetus, particularly of the heart. Whether other virus infections have similar deleterious effects is not known. It is obvious that all effort should be made to protect a pregnant woman against these infections during the early months and that, if she develops German measles, therapeutic abortion

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should be seriously considered. Similarly, there is ground to suspect that prompt, adequate ventilation of the lungs at birth may be helpful in closing the ductus arteriosus and preventing the persistence of patent ductus arteriosus. The public health campaign against venereal disease, together with the improved facilities for early diagnosis and treatment of syphilis, has already resulted in a striking decrease in the incidence of syphilitic heart disease. It is not too optimistic to look forward to a time in the not distant future when syphilitic heart disease will be as rare as leprosy. Likewise, the use of penicillin and other antibiotics before and after tooth extractions and other surgical procedures involving the possible spread of infection should be advised for all vulnerable individuals, in the hope of preventing bacterial endocarditis. It is the responsibility of the physician to see that patients with rheumatic valvular disease or certain congenital abnormalities of the heart receive this advice. It is possible, though not yet proved, that the administration of penicillin or similar drugs, either at the very onset of streptococcus infection or given prophylactically for long periods of time, may decrease the incidence of chronic rheumatic valvular disease. What lies ahead as a result of the present work on ACTH and cortisone and other researches, we all await with great interest and hope.

When it comes to the two major types of heart disease, hypertensive and coronary, there is little of definite prophylactic value that is known at present. The psychosomatic aspects of hypertension need further exploration. The same can be said concerning many other fields of study that bear on the nature and mechanism of hypertension and renal disease. Finally, the relation between diet, especially the ingestion of fats or cholesterol containing foods, and the development of atherosclerosis is a subject shrouded in mystery. Much research and the application of many different types of scientific disciplines will be necessary before these problems of prevention will be solved.

Diagnosis: While awaiting further methods of prevention and treatment of heart disease, the physician has the responsibility of utilizing the available resources and knowledge in the care of cardiacs. As is true in most fields of medical practice, the greatest difficulty is the question of accurate diagnosis. Once a case has been properly diagnosed, errors in treatment, though they still occur even in the best of hands, are not very numerous. The physician can quickly find out what medical or surgical procedures are applicable for a given condition. The difficulty arises if the original diagnosis is incorrect. These errors are particularly disastrous if curable or reversible conditions are overlooked. I propose, therefore, to discuss some of the difficulties in cardiac diagnosis that I encounter and to comment on the mistakes I have made myself or that I observe to be going on in general practice.

Congenital Heart Disease: The present surgical treatment of various forms of congenital heart disease now demands that the physician be alert to those abnormalities that are curable. There are some simple clinical clues that we all can employ in detecting these cases and guiding them to

appropriate surgical clinics for treatment. Cyanosis, with or without clubbing of the fingers, and polycythemia are obvious signs that need investigation. In fact, if one is sure that there is no cyanosis, a shunting operation is not likely to improve the situation. Any unexplained murmur, or abnormal configuration of the heart on roentgen-ray examination, in an infant, child or young adult must make one think of the possibility of congenital heart disease. When this question arises, further study by trained observers, including catheterization of the heart or angiocardiography, may be necessary to establish a correct diagnosis. At present the four conditions especially to keep in mind are patent ductus arteriosus, tetralogy of Fallot, coarctation of the aorta and abnormal vascular rings at the base of the heart.

I have overlooked a simple case of patent ductus arteriosus, regarding the condition as an inconsequential pulmonary systolic murmur, because my auscultation was too hasty and the faint diastolic component to the murmur was not detected. During the past six months I saw two adults in the early twenties both of whom had been examined many times before and yet in neither case had any diagnosis been established. On careful auscultation, especially with the patient taking deep breaths, a definite faint continuous murmur was audible in the pulmonary area. In each instance cures were obtained by surgical section of the patent ductus. The diagnosis in such cases is not difficult if the physician trains himself to carry out careful auscultation and is aware that not all cases of patent ductus will show loud machinery murmurs.

The diagnosis of coarctation of the aorta is in a sense even more important. When patent ductus is overlooked, the eventual complications may still direct attention to the gravity of the situation. The child may remain underdeveloped, symptoms of cardiac insufficiency may appear, or bacterial endocarditis may intervene. Even then the condition may be amenable to treatment. In coarctation of the aorta, sudden catastrophies such as rupture of the aorta or cerebral accidents may take place without warning in patients who previously were in fairly good health. It is, therefore, necessary to suspect this diagnosis in every case of hypertension and to feel for pulsations in the abdominal aorta, femoral and dorsalis pedis arteries. If these peripheral pulsations appear to be vigorous one can fairly safely dismiss the diagnosis, but if not, blood pressure determinations of the legs and roentgenogram of the chest should be obtained looking for further evidence of coarctation of the aorta.

In a very recent case I unfortunately overlooked the diagnosis in a child of eight who appeared to have adequate peripheral pulses and who showed blood pressure readings in the legs equal to those in the arms. The child died abruptly of a rupture of the thoracic aorta just below the point of coarctation. In retrospect, the diagnosis might at least have been suspected and possibly more firmly established if greater attention had been paid to the slight elevation of blood pressure in the arms. In this case the readings were 130/90, which are higher than normal for such a young child. The

tragic aspect of this experience is that the condition might have been cured if the proper diagnosis had been made.

Little need be said in this discussion about tetralogy of Fallot or the other cyanosed congenital cardiacs. The problem of accurate anatomical diagnosis may be difficult, but the finding of obvious cyanosis, polycythemia, clubbing of the fingers, tendency to squat, roentgen-ray and electrocardiographic study, all within the reach of most practitioners, can quickly filter the cases that might be helped by a Blalock-Taussig operation. If the electrocardiograms show left axis elevation or hypertrophy, one can quickly eliminate tetralogy of Fallot from consideration and entertain the possibility of tricuspid atresia with rudimentary right ventricle. In rare instances infants may appear cyanosed from drinking polluted water and developing methemoglobinemia, a condition that is readily reversible by eliminating the cause. Similarly, congenital familial methemoglobinemia may be confused with congenital heart disease. I saw one such man, 20 odd years old, who had been blue since birth and was regarded as having some form of congenital heart disease. He was found to have methemoglobinemia and, within one half hour after being given methylene blue, changed to a normal pink color for the first time in his life. Finally, I have seen several patients suffering from argyria, brought on by injudicious and prolonged use of silver nose drops, who were regarded for years as having congenital heart disease.

During the past several years, Gross and his colleagues have brought to our attention a group of conditions in which the aorta and its branches are malformed, that are amenable to surgical cure. There may be a double or right aortic arch, or one of the main arteries coming off the arch may traverse an abnormal course. Some of these are symptomless, but others produce choking, dyspnea, dysphagia, chronic cough or repeated respiratory infections. When these clinical features are observed in an infant, the possibility of abnormal vascular rings at the base of the heart must be considered. Careful roentgen-ray study in competent hands can generally establish the diagnosis, and appropriate surgery may be curative and even life saving.

Rheumatic Heart Disease: The diagnosis of rheumatic heart disease may be divided into two phases, i.e., the recognition of acute rheumatic fever or active rheumatic state, and of chronic rheumatic valvular disease. Typical acute rheumatic fever or chorea would hardly escape the attention of the average physician. However, the atypical cases will remain difficult to detect until we have a more specific and pathognomonic test that identifies this disease. For the present, I feel convinced that simple infections or sore throats that ordinarily come and go without mishap may be the trigger that initiates rheumatic heart disease in some vulnerable individuals without any ordinary evidence of arthritis or chorea. This brings up the entire question of the internal environment of the host as an important factor in determining whether any particular insult, bacterial or otherwise, will result in a rheumatic response. Many years ago, in speculating concerning the

nature of rheumatic heart disease,[1] I suggested that the endocrines may have a significant bearing on whether a given patient will suffer a rheumatic or cardiac bout following a particular infection. This view is gaining considerable support from the observations that the adrenal hormones profoundly affect rheumatic fever and rheumatic carditis. What this new approach, initiated by Hench and Kendall, may lead to in the future remains to be seen. There is reason to believe that much will come of it.

There is little that I can add to the current views concerning the diagnosis of active rheumatic fever. We are all making errors of omission and commission. There must be many illnesses unassociated with limb pains that are "rheumatic" and, contrariwise, we now know that other infections frequently produce transient and rarely serious and even fatal injury to the heart. This past year I overlooked an instance of acute and subacute rheumatic carditis in a man 68 years old who was not aware that he previously had had rheumatic fever and yet who showed, on postmortem examination, an old rheumatic aortic stenosis and evidence of acute rheumatic myocarditis and endocarditis. If an acute illness, generally febrile, is accompanied by vague symptoms and is followed by the development and persistence of a significant murmur, it is quite likely that the patient is rheumatic. Now that antibiotics are used so freely it is quite possible that some such illnesses are abortive instances of bacterial endocarditis with recovery.

The diagnosis of rheumatic valvular disease is still imperfectly made. Although there are many procedures that are employed, including electrocardiography and roentgenography, what is least proficiently practiced is the clinical bedside method. In this regard the art of auscultation has suffered the most. The presence of the tell-tale diastolic or presystolic murmur of mitral stenosis is still often overlooked. The same is true of the faint diastolic murmur of aortic insufficiency. With training and careful use of the simple stethoscope, many diagnoses can be made that at present are being missed. One must start with the right stethoscope, avoid haste in auscultation, and do away with extraneous noises in the examining room. I cited the cases in which the continuous quality of the murmur of patent ductus was not detected for many years. I have seen instances of bacterial endocarditis which were supposed to be unaccompanied by any murmur, only to demonstrate a definite aortic diastolic murmur when auscultation was carried out with the patient upright and during a held expiration. Although there is much to be desired concerning the interpretation of systolic murmurs, I can not emphasize too strongly the diagnostic importance of auscultation of the heart.

Hypertensive Heart Disease: The diagnosis of hypertensive heart disease does not present many difficulties. The determination of the blood pressure and ophthalmoscopic examination generally suffice. It is important to give some thought to the rare possibility of a pheochromocytoma or coarctation of the aorta, for they are curable conditions. At times, cardiac enlargement and heart failure are due to a previous long standing hypertension

in which the blood pressure may be within normal range. Under those circumstances the fundi are likely to reveal evidence of previous hypertension. It is still difficult to explain why some hearts become enlarged or fail at one pressure level and others remain competent or show little if any hypertrophy after a much longer time or with higher levels of pressure. Whether some of these patients when quiet or asleep maintain a much lower or normal pressure level than others, or whether patients have different types of coronary arteries and capillaries, remains obscure. In fact, the entire problem of cardiac hypertrophy presents aspects that are puzzling.

Coronary Artery Disease: Great progress has been achieved in the diagnosis of disease of the coronary arteries. The classical history of angina pectoris, which practically always denotes coronary sclerosis, generally is diagnostic. Difficulties arise when the symptoms are atypical. The anoxemic test or the exercise tolerance test may occasionally help to differentiate coronary disease from other conditions. Electrocardiography may be of inestimable value. When the primary distress is not definitely related to effort, especially walking, one has reason to doubt the diagnosis of angina. However, I have made occasional errors in dismissing the diagnosis of angina when recurrent pain in the chest was in no way related to effort and all other findings were negative. There is one test that may be performed if a patient is seen while he has pain. At that moment, carotid sinus stimulation will practically always lessen the pain or make it disappear entirely, if the heart is significantly slowed. In fact, if pain is not altered by marked slowing the pain is very unlikely anginal, and if it disappears in 10 to 15 seconds it is almost certain that it is anginal. If no slowing results, no conclusion can be drawn. These observations have occasionally been decisive in arriving at correct diagnosis.

There are many patients who have coronary pathology which is overlooked because they have other primary complaints and do not mention the fact that during the previous year or two they had slight sternal discomfort or pressure on hurrying. I have occasionally been unaware that a patient who was to have some surgical operation really had had angina pectoris for several years previously, until at some later date he suffered a coronary thrombosis. Only then was the early history of a sternal constriction on effort elicited on direct questioning. It is necessary, therefore, to make a deliberate inquiry concerning this point.

The diagnosis of coronary thrombosis with myocardial infarction is nowadays a simple matter in most cases. Errors do occur in both directions and some are unavoidable, though the number is steadily decreasing. This is the one condition in which recent developments in electrocardiography have been of greatest service. Although the clinical appraisal of the problem is generally adequate, in doubtful cases serial electrocardiograms may help greatly. There is still danger in reading too much into the tracings. I wish particularly to direct attention to the confusion between acute posterior myocardial infarction and acute cor pulmonale. I have been misled in the

past in this differentiation. During the past few years I became involved in two identical medico-legal controversies, in which workmen were supposed to have suffered fatal coronary thrombosis about two weeks after some accidental injury. In both cases the diagnosis of posterior myocardial infarction was supposed to have been confirmed by typical electrocardiographic changes. Insurance was denied the widows because the coronary attacks had occurred so long after the injury to the legs. I advised that the bodies be disinterred and that autopsies be performed, although it was several months after burial. I suspected that the entire condition could be explained on the basis of thrombophlebitis and pulmonary embolism, as that is a much more common post-traumatic complication than coronary thrombosis. Examination confirmed the suspicion and showed the coronary arteries to be normal. Many authors have called attention to the great variety of conditions which may be confused with coronary thrombosis. They all, at one time or another, need to be considered when the case is atypical.

Miscellaneous Forms of Heart Disease: There remains a miscellaneous group of cardiac conditions, less common than the above, to be sure, but often of great importance because the disability is curable or reversible. Amongst these are those suffering from masked thyrocardiac disease. One must constantly keep this question in mind, either as the sole cause of heart disease and heart failure or as an additional load in a patient already suffering from some other type of heart disease. Although the clinical appraisal is generally adequate, in doubtful cases other tests will be necessary apart from the basal metabolism determination, such as the radio-active iodine uptake or the estimation of the protein bound iodine in the blood. Needless to say, appropriate treatment affords excellent results and at times complete cures.

Another uncommon remediable type of heart disease is constrictive pericarditis. Whenever a patient appears to have heart failure, particularly of the right side, with increased venous pressure and an enlarged liver, and shows insufficient evidence of valvular, hypertensive or coronary disease to account for his disability, one should think of constrictive pericarditis. Once suspicion has been aroused, further study, including roentgen-ray examination, ought readily to establish the diagnosis. Similar suspicion should arise if a patient has what appears to be cirrhosis of the liver with ascites, has no alcoholic history, and shows an increased venous pressure in the arms.

There is a small number of patients who suffer from heart failure that results entirely from an uncontrolled rapid arrhythmia. Generally this disturbance is auricular fibrillation, but rarely it may be paroxysmal auricular or ventricular tachycardia. Such patients may be seriously ill with pulmonary congestion and right sided failure. When auricular fibrillation is present and the heart rate is first slowed with digitalis and then the rhythm is regularized by the use of quinidine, the heart and circulation may return entirely to normal. I have also seen a few such instances in which the cause

of the rapid rate was prolonged paroxysmal auricular or ventricular tachycardia. This is a real, though uncommon, type of curable heart disease. The inference is that when a patient has heart failure every effort should be made to determine the etiology, and one should be ready to make the diagnosis of "cardiac arrhythmia without other evidence of heart disease," even if advanced failure with dilatation of the heart is present, when no other cause can be found.

There has been an increasing awareness of a group of patients who suffer from right sided heart failure and decreased arterial oxygenation resulting from chronic disease of the lung or pulmonary arteries. These include cases of emphysema, silicosis, marked thoracic deformity, pulmonary arterial disease of unknown origin, and other disorders of the lung. They all develop breathlessness, with or without cough, and eventually right ventricular enlargement and failure. As a group they do not respond well to cardiac therapy but may be helped by measures directed at the bronchi, lungs and diminished oxygenation of the body.

Numerous other rare types of heart disease can be enumerated which need to be considered when one is presented with cases that do not fall readily into the more common groups. Amongst these is heart failure from an A–V aneurysm, either in the lungs or in the periphery of the body. The detection of a continuous murmur will establish the diagnosis. The condition can be cured only by surgery. Another curable form is beri-beri heart disease. This must be suspected in alcoholics or in those who have been living on a poor diet. The therapeutic response to thiamine is dramatic. Still other types of heart disease are scleroderma heart, amyloid heart, atypical forms of myocarditis, including Fiedler's myocarditis, lupus erythematosus disseminatus, parasitic involvement of the heart, tumor of the heart, ruptured valves, the heart in Addison's disease, myxedema heart, etc. It is obvious that in atypical cases a great variety of causes must be considered, some reversible and others incurable.

Treatment: Once a correct diagnosis is established, treatment is likely to be carried out satisfactorily. The most common error is for patients to be treated for one form or another of heart disease when the heart is normal. This is particularly true when functional or non-cardiac symptoms are misinterpreted as due to angina or coronary sclerosis. There are many patients with gross abnormalities of the electrocardiograms, even showing bundle branch block, who are essentially well and require no cardiac therapy. A second common error is to treat patients with definite organic heart disease, either valvular or myocardial, as if they have heart failure when there is no decompensation. Patients with hypertension or valvular disease carry on well compensated, with or without cardiac enlargement, for many more years than they do in the stage of decompensation. They are often disturbed and in no way helped by injudicious use of digitalis and by unwise prohibitions during these many years of cardiac compensation. Active therapy should be directed at the threatened or actual presence of congestive failure.

Before instituting a program of treatment for a cardiac, the physician should consider carefully all those unusual conditions enumerated above for which specific curative therapy, medical or surgical, might be applicable. The second consideration is to decide whether congestive failure is present. At times this decision is difficult. Pulmonary râles may be due to infection, infarction or tumor. Peripheral edema may be due to nephritis or incompetent veins in the legs. An enlarged liver may be due to cirrhosis or cancer. In some cases careful study, including measurements of the dynamics of the circulation, will be necessary to distinguish cardiac failure from these other conditions.

When the patient is actually suffering from congestive failure, whether it be valvular or non-valvular in origin, the present day therapy that is being practiced is generally well directed. I shall not elaborate on the common procedures employed, such as the use of digitalis and diuretics. I do want to mention a few points that I believe need emphasis. The first is that many cardiacs are kept in bed too long and are given too lengthy periods of convalescence. I have been increasingly convinced that patients with congestive failure, especially those primarily suffering from dyspnea, are better treated in a chair than if confined to bed all day. Furthermore, the bed in which they sleep at night should have eight to nine inch blocks placed under the head posts so that gravity may tend to keep body fluids in the lower part of the body. There are abundant physiological and clinical data to support this view. When convalescence sets in, too often patients are told to keep away from work for many months, with disastrous results to their psyches and their economic status and with little if any gain in their physical condition.

There are certain details of medical management that are not uncommonly overlooked. Too frequently, cardiacs will have a liter or more of fluid in the pleural cavities that should be removed by paracentesis. Slight degrees of hydrothorax may respond to ordinary therapy, but there are some who will not start improving until a chest tap is performed. Likewise, in elderly males, a distended bladder may not be detected, the expected diuresis having occurred but been retained. I recall many cases in which large amounts of fluid in the bladder or pleural cavities were first found on postmortem examination. Another therapeutic procedure that is not employed sufficiently is phlebotomy. Many congested cardiacs are helped considerably by simple blood-letting. This can also serve to replenish our oft depleted blood banks. A final error that is prevalent is to continue using mercury diuretics until the patient becomes refractory and to neglect to determine whether the blood chlorides have fallen too low. Such cases may be made worse and worse and yet may begin responding to further mercury injections if the blood chlorides are returned to normal by adequate administration of ammonium chloride or hydrochloric acid.

In summary, the physician's responsibility in the field of cardiology is to utilize all known methods of prevention of heart disease, which at present

are only too few, to establish an accurate diagnosis, and to institute appropriate therapy. It will fall to the lot of the general practitioner or internist at least to suspect the disorders at their earliest possible stage and, when necessary, to seek the advice of those specially trained for further diagnosis and treatment. Despite the magnitude of the problem that lies ahead, we can be proud of the accomplishments of the recent past and look hopefully to the immediate future.

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ANTIBIOTICS: YESTERDAY, TODAY, TOMORROW *

By CHESTER S. KEEFER, M.D., F.A.C.P., *Boston, Massachusetts*

To say that the discovery and development of antibiotics have completely revolutionized the management of infectious disease is to repeat a widely accepted statement. When one reflects that 10 years ago there were no antibiotics available for general use in man, and that today there are at least eight, it is a truly extraordinary state of change. These antibiotics include, in order of their discovery and use, tyrothricin, penicillin, streptomycin, bacitracin, polymyxin, aureomycin, chloromycetin, neomycin, and, most recently, terramycin. All of these antibiotics have a definite place in the the treatment of patients and in animal diseases. Today I shall review briefly, within the limitations imposed by time, some of the benefits that have accrued from antibiotics and discuss some of the trends of today and tomorrow.

Prior to the use of antibiotics, the most effective agents for the treatment of infections were pure chemical agents such as the arsenicals and the sulfonamides and specific antiserums. The chief difference between the mode of attack upon disease by means of antiserum and chemotherapy was the great specificity of antiserum. This specificity was sharply defined insofar as antibacterial action was concerned: antiserum had to be so developed and produced that it was specific for single serological types of bacteria. Pure chemical agents, on the other hand, had a much broader action, so that the sulfonamides were not only active against one group of bacteria but had a powerful effect in varying degree against a wide variety of bacteria. It is still a mystery how microörganisms are inhibited in their growth and finally die after being exposed to an environment in which there is a high concentration of an anti-infective agent, but there is general agreement that these chemical agents interfere in some way with the normal growth and metabolic processes of the bacteria.

What has been said for the pure chemical substances, such as the sulfonamides, also applies to the anti-infective agents derived from microbes, namely, the antibiotics. Here the action of the antibiotics is broad in that more than one group of bacteria is attacked by a single antibiotic. It is true, however, that certain patterns have developed tending to define the groups of microörganisms affected most often by different antibiotics. For example, it is quite clear that penicillin exerts its action in a most powerful way against gram-positive cocci, against Treponemal infections, and against gonococci. It has either no effect or a very feeble effect against all gram-negative bacilli. Streptomycin, on the other hand, has a striking effect against the tubercle bacillus and against many gram-negative bacilli; its ef-

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fect against the Treponemata and against gram-positive microörganisms is much less than penicillin. It is for this reason that streptomycin or dihydrostreptomycin are used almost exclusively for the treatment of tuberculosis and sensitive gram-negative bacilli. It is a striking fact that neither penicillin nor streptomycin has any effect upon the common virus infections or upon rickettsial infections.

In the case of aureomycin and chloromycetin, the action of these drugs is different from either penicillin or streptomycin in that they have an effect on bacterial infections as well as on some virus diseases and rickettsial infections. For example, aureomycin inhibits the growth of both gram-positive as well as gram-negative organisms, but it is somewhat more active against gram-positive organisms than against gram-negative bacilli. Chloromycetin, on the other hand, while active against both groups of organisms, is more powerful against gram-negative organisms. This is evidenced in a striking manner in the treatment of typhoid fever. Here chloromycetin is the more effective drug. Both aureomycin and chloromycetin are equally effective against primary atypical pneumonia, lymphogranuloma venereum, granuloma venereum, acute brucellosis and the rickettsial diseases (typhus fever), and amebiasis.

We can see, then, that with the development of each new antibiotic additional diseases are brought under control, and the number of antibiotics that are capable of influencing common infections in varying degrees of effectiveness is multiplying. This is important, because it has become increasingly clear that, while one antibiotic such as penicillin may control 85 per cent or more of infections such as staphylococcic infections, there are a number of such infections that resist the action of penicillin but will respond to another antibiotic, such as streptomycin, within a few days. If this resistance asserts itself before the maximum effect of the drug has been obtained, then it is imperative that the condition be recognized and a new antibiotic substituted. It is a comfort to know that there is more than one antibiotic that is active against the same type of bacterial infections, and that organisms that are resistant to one antibiotic may be sensitive to another. At the present time, there is no way of predicting prior to treatment whether a given infection will be sensitive or resistant, unless the organism is tested for sensitivity before treatment is started. If this is not done, then the clinical response to treatment is the best guide.

So far I have said something about the differences between penicillin, streptomycin, aureomycin and chloromycetin. I shall now turn attention briefly to bacitracin and polymyxin. Bacitracin has the same general bacterial spectrum as penicillin, that is to say, it is more active against gram-positive organisms than against gram-negative bacilli. Organisms that are resistant to penicillin may be sensitive to bacitracin. Bacitracin has been used most extensively in the treatment of mixed infections of wounds after penicillin and streptomycin have failed to bring the infection under control. When bacitracin is given by mouth amebiasis can be controlled; and it is

effective in pneumococcic lobar pneumonia when given parenterally. Due to the fact that some samples of bacitracin have been nephrotoxic, most of the bacitracin has been used locally. However, it can be used systemically in patients with serious infections due to penicillin resistant organisms.

Polymyxin (Aerosporin) is not a pure substance, but it is highly specific against gram-negative bacterial infections. So far, it is the most powerful agent against *some* strains of *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*). One of the drawbacks against its use is the fact that many of the batches of material are nephrotoxic.

Terramycin is the most recent antibiotic to be added to the list. The experience with its use is limited, but it would appear that it has the same general bacterial spectrum as aureomycin and chloromycetin but that its effect upon gram-positive organisms is greater than against gram-negative bacilli. Patients with rickettsial infections, primary atypical pneumonia, acute brucellosis, and pneumococcic pneumonia have responded favorably. Failures have been recorded in salmonellosis and in typhoid fever. From the evidence that has accumulated so far it would seem fair to say that terramycin will take its place along with the other antibiotics, and that its effect will probably be similar to aureomycin and chloromycetin, but that it will not be as effective as chloromycetin in typhoid fever.

Synergistic Effects

An extremely important subject about which very little reliable information exists, especially with respect to the treatment of human infections, is the question of synergistic effects of antibiotics. That is to say, is it possible to obtain synergistic effects by using two antibiotics simultaneously for the treatment of an infection? Experimentally it has been demonstrated that penicillin and bacitracin have a synergistic effect in rabbit syphilis. Also, it has been demonstrated that penicillin and streptomycin have a synergistic effect against strains of the enterococcus; and in some patients with subacute bacterial endocarditis due to the enterococcus, recovery has been recorded following the use of both penicillin and streptomycin after penicillin alone has failed. On the other hand, penicillin and chloromycetin had the opposite effect, namely, that the full action of penicillin was not demonstrated when chloromycetin was added to the culture medium. This whole question of synergistic effects needs rigorous experimental study because there are still some common bacterial infections that cannot be controlled adequately by any available antibiotic. Pyocyaneus infection is a good example of this type of infection.

Bacterial Resistance

I have already referred briefly to the occurrence of bacterial resistance. This subject is one of the most important today. The evidence suggests, of course, that some strains of different bacteria can be made resistant to almost all antibiotics provided the organisms are exposed to the antibiotic long

enough. For example, it is known that gram-negative bacteria develop resistance to streptomycin rapidly but to aureomycin and chloromycetin much more slowly. Also, organisms develop resistance to penicillin in vitro very slowly, and, indeed, penicillin is so active against some bacteria that it has been almost impossible to develop or demonstrate penicillin-resistant strains of such an organism as the gonococcus. At the present time, then, it will be well in the use of any of the antibiotics to attempt to obtain the optimum results of treatment as promptly as possible by exhibiting adequate doses of penicillin promptly.

There is another problem that is intimately associated with the subject of resistance, and that is the question of superinfection occurring during the course of the treatment of patients with a specific disease. This subject has been reviewed by Weinstein in our clinic. It has been pointed out by Weinstein and others that, following the use of one antibiotic such as streptomycin for the treatment of *Hemophilus influenzae* infection, it is possible to bring the influenza bacillus infection under control but that the patient then shows the signs of a staphylococcic infection which must be treated by penicillin. Here, it would appear that when one group of organisms is suppressed, others that are present may persist, multiply and invade tissues and cause a superinfection. Unless this situation is recognized and the treatment changed, disastrous results may follow. Moreover, an infection may be declared resistant when it is susceptible provided the correct antibiotic is used.

Hypersensitivity to Antibiotics

Before discussing hypersensitivity to antibiotics, I want to say something about hypersensitiveness in general. It was just 45 years ago that von Pirquet and Schick published their classical monograph on serum sickness. Since that time this problem has received constant attention because of its frequency and importance. Very briefly, it has been shown that, following the injection of horse serum into man, the antigen can be detected in the circulating blood for a variable period of time. Beginning about the fifth to the fourteenth day after injection of the complex protein, antibodies begin to appear in the circulating blood. At this time, the classical clinical features of serum sickness appear. They are a gradual increase in body weight with edema from retention of sodium chloride and water; enlargement of the lymph nodes and spleen; various skin eruptions; and, finally, fever, leukocytosis, and arthralgias. As the antibody titer of the blood increases, the antigen titer decreases and the symptoms subside. With the disappearance of antigen from the blood the clinical symptoms disappear and the patient recovers. However, antibodies continue to remain in the blood and tissues for long periods of time. In some patients, the foreign protein may remain in the circulating blood for many weeks and antibodies fail to appear. In these patients, serum sickness fails to develop.

The antibody in patients with serum sickness is *heat stabile* and, when

present in the blood, is demonstrable in vitro by the usual immunologic technics, and in vivo by anaphylaxis, the Arthus reaction, the immediate type of cutaneous reaction with wheal and flare, and the capacity to sensitize passively. Sensitivity can be detected in such a patient by passive transfer, and by positive reactions to scratch or intracutaneous tests.

There is a second form of allergy or hypersensitiveness in which the antibody is *heat labile*. It never reacts in vitro, but is capable of producing prolonged passive sensitization of tissues, especially of the skin into which it is injected. This antibody may develop in anyone under suitable circumstances. It is most often demonstrated in so-called "atopic" persons.

There is a third form of hypersensitive patient in whom no demonstrable antibody is found in the circulating blood. This is the commonest form of allergy to drugs and infections. There may be a tuberculin type of reaction in the skin following the injection of the allergen, or a local superficial reaction may often follow a patch test, or a general reaction when the antigen is absorbed into the circulation. Sensitiveness to antibiotics usually falls into this group.

Penicillin Sensitivity

The reactions following penicillin therapy are those of contact dermatitis, or they are analogous to serum sickness. Rarely, the reactions are severe and resemble angioneurotic edema, and acute anaphylactic shock with asthma. The mucous membranes of the mouth and throat become sensitized to penicillin following the use of troches or lozenges.

A wide variety of reactions to penicillin has been recorded and reviewed. From an analysis of the reported cases in the literature, the following conclusions are justified: Reactions occur most frequently in patients who have had several courses of penicillin. The continuation of penicillin treatment of a patient who has reacted to penicillin with urticaria may or may not be tolerated. Skin tests are unreliable in predicting the occurrence of reactions, and the antihistamine drugs may or may not control the reactions and permit the continuation of penicillin therapy.

It is reasonably clear that hypersensitive reactions arise most often following its application to the skin in the form of ointment, especially when the skin is inflamed. Sensitization is also very common following the instillation of penicillin into the conjunctivae. It is least common following oral administration. Following intramuscular injection of aqueous solutions, the incidence of hypersensitivity is about 3 per cent. Following the injection of penicillin in oil, especially when combined with wax, the incidence of reactions is higher and varies from 5 to 7 per cent of cases.

There is another type of reaction following penicillin which was recognized early in its use and which deserves comment—that is, reactions in the skin at the site of previous trichophyton infections following the injection of penicillin. There is evidence that there are cross reactions between penicillin and certain strains of trichophyton. Cormia, Lewis, and Hopper have

demonstrated cross reactions between penicillin and trichophyton in animals, and express the opinion that there is a common antigen in these two materials.

Also, it has been demonstrated that some patients who receive penicillin in heparin or in beeswax may become sensitive to either the heparin or the beeswax.

It seems plain, then, that a certain number of patients become sensitized to penicillin. In some, the reactions are analogous to serum sickness; in others, the reactions are those of contact dermatitis, or Arthus' phenomenon, or acute anaphylactic shock. Because a patient has become sensitized locally (i.e., contact dermatitis), the future use of penicillin is not precluded, since less than 1 per cent of such patients will react after systemic injection of penicillin. Once a patient has become sensitized to penicillin following systemic injection, he may have an accelerated reaction following a second injection or he may have *no reaction.* The time that elapses between the first and second injection is important, i.e., the longer the time, the less likely the reaction.

Streptomycin

As in penicillin therapy, skin eruptions are observed following streptomycin in about 5 to 7 per cent of patients. The reactions are often transitory, so that when the patient continues to require treatment for his infection, the streptomycin can usually be continued and the eruptions will disappear. In about 15 per cent of patients, once the rash appears it continues to become worse, and in these patients it is necessary to stop the streptomycin. The duration of the rash is between one and eight days in most patients when the streptomycin is continued. In those in whom the streptomycin is discontinued, it disappears in one to three days in about two-thirds of patients, and within a week in about 20 per cent, but it lasts about two weeks in 10 per cent of patients. Fever occurs with skin eruptions in about a third of the cases.

Other signs of allergic reactions following streptomycin are eosinophilia and arthralgias.

The most disturbing and the most serious reactions following streptomycin are the reactions of the eighth nerve, vertigo, tinnitus, and deafness. With the improvement in the purity of streptomycin and with the development of dihydrostreptomycin, the incidence of these features has decreased. It is extraordinary that the latent period between the injection of streptomycin and the development of eighth nerve disturbances has varied greatly with the preparations that have been used. During the early period of clinical investigation, when relatively impure streptomycin was used, the majority of eighth nerve disturbances were observed within the first two weeks of treatment. The overall incidence was 6.9 per cent. Later, when prolonged treatment was employed for tuberculosis, the incidence was much higher, but the latent period between the onset of treatment and the development of neurological disturbances was longer, averaging 17 to 21 days. It

seems quite plain at present that patients who receive streptomycin for less than two weeks rarely develop eighth nerve disturbances. About 15 to 20 per cent of patients with tuberculosis who receive 1 gm. a day for 42 days may develop vertigo. With dihydrostreptomycin, the incidence is lower on these dosage schedules.

Treatment of Drug Allergy

In general, it can be said that the treatment of drug allergy is unsatisfactory. It consists of withdrawal of the drug and symptomatic treatment. The duration of symptoms and signs of allergy varies greatly, from a few days to six or more weeks, depending upon the type of reaction.

Symptomatic treatment has improved with the introduction of antihistamine drugs. These drugs relieve the skin eruptions, especially the urticaria and the itching. They are less effective in controlling the arthralgias if they are present. The antihistamine drugs are also local anesthetics, so that some of them relieve itching when applied locally.

Injections of epinephrine and ephedrine by mouth are also helpful for acute urticaria and itching. The use of 4 per cent benzyl alcohol as a local anesthetic is likewise useful.

Attempts at desensitization are usually wholly unsatisfactory.

The time factor is very important in deciding whether a patient will react to a second injection after he has had experience with a first injection. The longer the interval of time between the use of a drug like penicillin, the less likely the patient is to show immediate and accelerated reactions. In the case of sensitivity to penicillin or streptomycin, it is often possible to continue the drug in spite of a skin eruption. In the case of other drugs this is not possible and they should be discontinued at once.

If it is known that patients have had a previous reaction to a drug, a similar drug should not be administered a second time without the necessary precautions; that is to say, a small test dose of the drug might well be given. If no reaction to the test dose occurs, then one may proceed with treatment cautiously.

The Antibiotics of Tomorrow

It is not too far fetched to hope that new antibiotics will be discovered and developed that will improve our position with respect to the treatment of some of the bacterial and other infections for which there is now no adequate treatment. For example, we need very much indeed new agents for the treatment of tuberculosis, agents that are non-toxic and that can be taken by mouth for long periods of time without the bacteria becoming resistant. Antibiotics are needed that will control pyocyaneus infections, all proteus infections, and salmonella infections. Also, there is a crying need for anti-viral agents and anti-fungicidal agents, as well as new agents for protozoal and parasitic infections.

There are good reasons for believing that such agents will be found.

The microbiological laboratories of universities, of industry and of government are expending large sums of money, time and effort in order to wage war on disease. They deserve high praise indeed, since the benefits extend far beyond the humanitarian ones that are obvious to physicians and patients.

In brief, it can be said that the advances that have taken place in the field of antibiotics during the past 10 years are phenomenal. Greater medical advances have taken place in the past 10 years than at any other time in medical history. That these advances will continue, there seems to be no doubt.

THE TREATMENT OF INTRACTABLE PEPTIC ULCER*

By Walter L. Palmer, M.D., F.A.C.P., Joseph B. Kirsner, M.D., F.A.C.P., and Irwin Levin, M.D., *Chicago, Illinois*

The term "intractable" means "difficult to treat" or "unruly." The conclusion that a given patient or a given ulcer is "intractable" is in part at least a matter of opinion. It is important to distinguish between intractable people and intractable lesions. The more the physician strives to gain the coöperation of his patients and to understand them as individuals, the fewer will be the truly intractable ones. The treatment required for an intractable ulcer depends upon a number of factors: the coöperation of the patient, the location of the lesion, the amount of gastric secretion, the ease of neutralizing the acid, the rate of gastric emptying and the complications present. The various problems and their management may perhaps be set forth best by a brief presentation of a series of selected cases.

Intractable Patients or Intractable Ulcer?

A male machinist was admitted to the hospital in 1948 at the age of 33 because of periodic epigastric distress of the ulcer type for the past 10 years. He was obviously disgusted with medical management, boasted that he had consulted innumerable doctors and that he had used every treatment on the market in large amounts to no avail. His gastric secretory rate was high, the fasting 12-hour nocturnal secretion of hydrochloric acid varying from 950 mg. to 2,600 mg. (normal 650 mg., average duodenal ulcer 2,240 mg.).[1]

Roentgen-ray examination disclosed a minimal deformity of the duodenal bulb with no evidence of a crater (figure 1). A few months before admission to the hospital he had visited an excellent clinic and had been advised to undergo a subtotal gastrectomy. He refused this advice and came to our institution where a transabdominal vagotomy was performed. In the subsequent two years the original distress did not return but the patient complained bitterly of "belching, gas, lump in the stomach, and a tendency to diarrhea." The roentgen-ray findings were unchanged; the gastric tone and motility were normal. The insulin test was positive. With simple reassurance and explanation, the symptoms promptly disappeared. They may recur just as promptly.

Now what does all of this mean? Perhaps the patient had an intractable duodenal ulcer cured by vagotomy; if so, the roentgenologic evidence was certainly minimal. The patient was inclined to think that the post-operative symptoms, obviously not due to ulcer, were as bad as the ulcer. Does this mean that vagotomy is a bad operation? A different explanation of both the preoperative and the postoperative symptoms seems to us to be nearer

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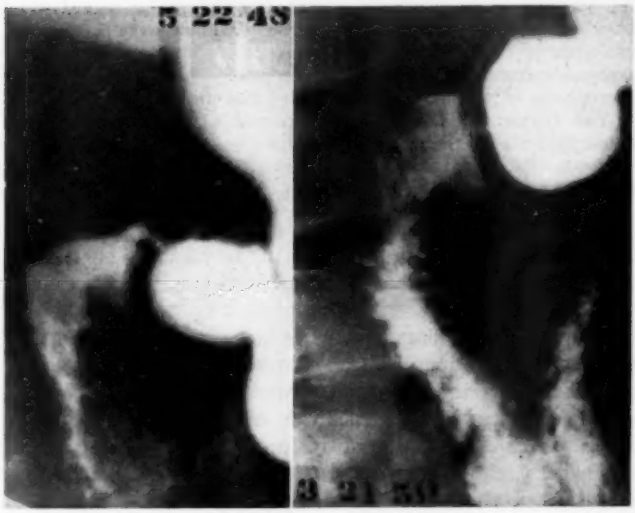

FIG. 1. L. B. Minimal deformity of duodenal bulb, no crater or stenosis before or after vagotomy. This patient should not have been considered to have an intractable peptic ulcer, nor to have been a failure of vagotomy.

to the truth. The patient, despite his rugged "he-man" appearance, had a rather hysterical personality. He had never established a good patient-physician relationship with any doctor. His suggestibility is indicated by the fact that when he was given a hypodermic placebo during the day with the statement that it would put him to sleep, he fell asleep in 10 minutes and did not waken for three hours. He was both bombastic and suggestive. The psychiatrist would doubtless have seen in him the classic conflict between striving for independence and the need for dependent gratification. It seems to us that if the patient-physician relationship had been adequate, the patient would have done well on almost any form of ulcer management. He was not unruly; his ulcer was small, producing only a slight deformity of the bulb and with no evidence of a crater. Consequently, we are reluctant to consider him as a truly intractable patient; likewise, the ulcer should not have been intractable.

The story of a surgeon seen in 1947 at the age of 65 is somewhat similar. Periodic gnawing epigastric distress had been present since 1902. He had been treated for ulcer by Dr. Sippy. An exploratory laparotomy in 1913 failed to disclose a lesion. The distress continued to recur. In 1941 a duodenal ulcer was demonstrated by roentgen-ray. An episode of bleeding occurred in 1943. In 1945 the ulcer was again demonstrated. In 1947, the distress having persisted, a minimal deformity of the duodenal bulb was again found radiologically; a crater was not seen. Here again the fasting 12-hour nocturnal secretory rate of hydrochloric acid was high, 2,050 mg., slightly less than the average for patients with duodenal ulcer. The patient was cer-

tain that his symptoms were due to a duodenal ulcer and that he needed an operation; a transabdominal vagotomy and posterior gastroenterostomy were performed. Within a few weeks after operation there was a recurrence of symptoms, distention, belching, slight diarrhea, depression, introspection, and remorse over the operation. He heard numerous criticisms of vagotomy and concluded that the operation had been a great mistake. With reassurance and detailed discussion of the situation, the symptoms were temporarily relieved. However, the patient has continued to complain of abdominal distress. Recently an episode of bleeding occurred, but no lesion could be demonstrated roentgenologically.

It does not seem proper to look upon this patient as one with an intractable duodenal ulcer. He has been difficult to manage, but the ulcer is a minor aspect of the problem. He is an overworked, depressed, elderly surgeon who has not learned how to live or how to take care of himself; as retirement approaches he does not know how to let go. The psychiatrist would describe the situation in different words; perhaps again he would see here the conflict between the dependent needs of the patient and his intense drive for independence; independence was achieved but the dependent needs were not gratified. The solution of this problem probably would have come not from powders or pills or operations, but from a better understanding of the emotional aspects, a better patient-physician relationship. The story is related to emphasize the importance of evaluating the total situation. The question of whether or not peptic ulcer is a psychosomatic disorder can not be considered here.

The Basis for True Intractability

Having now presented the stories of two patients considered to be intractable and treated as such surgically, yet who should not have been so had it been possible to establish an adequate patient-physician relationship, we may consider the question of what is true intractability. It must be admitted that there are patients with more or less persistent ulcer pain and persistent craters in spite of the conventional methods of treatment. One must insist upon the objective demonstration of a marked deformity or a crater as one of the methods of differentiating the patient with a truly intractable ulcer from the patient with a chronic dyspepsia, nervous indigestion, irritable bowel syndrome, or depression with somatic manifestations—a functional disorder of any sort. Given such a persistent lesion, the question arises as to the cause of the intractability. There are, of course, several causes, but in general they can be summarized by the statement that intractability is due to inability to accomplish adequate neutralization or inhibition of the acid gastric secretion, or to the presence of complication such as stenosis. Hence the treatment must vary from patient to patient and from lesion to lesion. In gastric ulcer the secretion of acid gastric juice is not excessive, whereas in duodenal and jejunal ulcers it is; nevertheless, in all lesions, reduction in acid secretion promotes healing as does better neutralization. The problem is that of methods and of complications.

Intractable Gastric Ulcer

Gastric ulcer differs from duodenal and jejunal ulcer in at least two important respects: the problem of cancer and the absence of hypersecretion. The differential diagnosis of benign and malignant ulcer can not be considered at this time; in general we take the view that there are no pathognomonic signs of benignancy whereas there are certain definite criteria of malignancy. Failure of a gastric ulcer to heal promptly on medical management may be evidence either of "intractability" or of neoplasm. Unless there are strong arguments to the contrary, such a lesion should be removed surgically. The practical problem is not that of neoplastic degeneration of a benign ulcer, for which there is very little valid evidence, but rather the difficulty in differentiating the two lesions.[2] The second way in which gastric ulcer differs from duodenal and jejunal lesions is in the lack of hypersecretion. It is important to point out, however, that if a sufficient number of histamine tests are carried out over a period of time, acid gastric juice can always be demonstrated; elevation of the pH to neutrality with constant reduction of peptic digestion is followed by healing of the ulcer; recurrence does not take place unless or until the acid secretion returns.[3]

Three brief case reports are illustrative:

A widow, now 78 years of age, developed ulcer distress at the age of 33 which subsided with conventional management but recurred from time to time. In the 10 years between 1936 and 1946 a gastric ulcer was demonstrated roentgenologically and gastroscopically on innumerable occasions. When complete achlorhydria was finally induced in 1946 by radiation therapy, the ulcer healed and has not returned to date, April, 1950 (figure 2).

On the other hand a laborer, now 61 years of age, developed ulcer distress in 1922 at the age of 33. Innumerable gastroscopic and roentgenologic examinations from 1936 to 1949 disclosed a persistent gastric ulcer. Strict antacid medical management would invariably produce a remission in his symptoms and a decrease in the size of the lesion, but it did not heal (figure 3). Three courses of radiation therapy failed to reduce the gastric secretion significantly. The lesion was finally excised in 1949. It is interesting to note that over the years the disability was not great because the symptoms were rather easily controlled by medical management even though complete healing was not accomplished. The failure seems attributable to inability to control adequately the pH of the gastric content.

Similarly, a retired policeman, now 66 years of age, experienced recurrent episodes of ulcer distress from 1934 to 1947. Roentgen-ray and gastroscopy in 1947 both disclosed gastric ulcer (figure 4). Ulcer management relieved the distress but the lesion did not heal. Radiation therapy resulted in only a transitory decrease in gastric secretion. The stomach did not empty properly; it was large, dilated, atonic, with no obvious site of obstruction; peristalsis was relatively inactive. Consequently, subtotal gastrectomy and vagotomy were carried out. The failure of medical management in this instance seems attributable again to inability to control peptic digestion; delayed motility and gastric retention of obscure etiology were doubtless significant contributing factors.

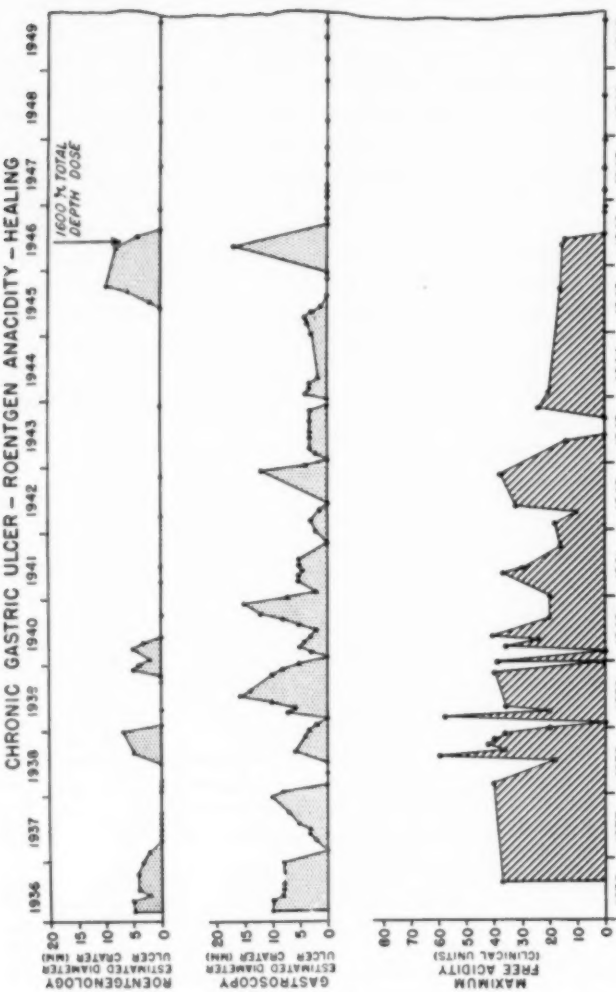

FIG. 2. A. K. Intractable gastric ulcer, 10 years. Complete healing; no recurrences following production of achlorhydria by radiation therapy. Each dot represents examination as specified.[7]

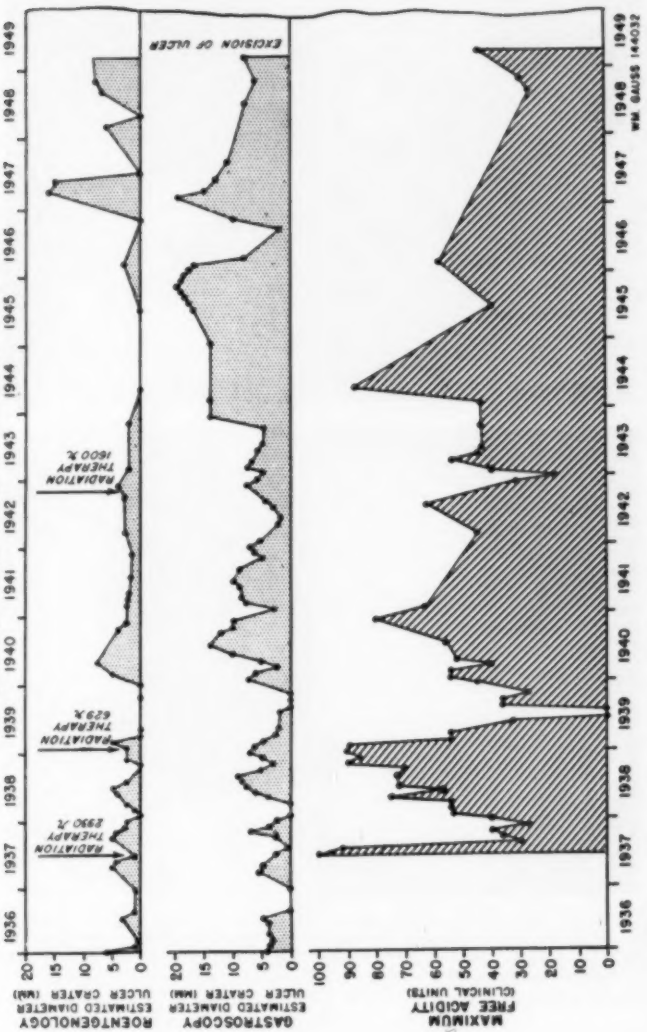
CHRONIC GASTRIC ULCER – UNHEALED – BENIGN
ROENTGENOLOGY
ESTIMATED DIAMETER ULCER CRATER (MM)
RADIATION THERAPY 2930 R
RADIATION THERAPY 629 R
RADIATION THERAPY 1600 R
GASTROSCOPY
ESTIMATED DIAMETER ULCER CRATER (MM)
EXCISION OF ULCER
MAXIMUM FREE ACIDITY (CLINICAL UNITS)
1936 1937 1938 1939 1940 1941 1942 1943 1944 1945 1946 1947 1948 1949

FIG. 3. W. G. Intractable gastric ulcer—from inadequate neutralization or reduction of gastric acidity.[2]

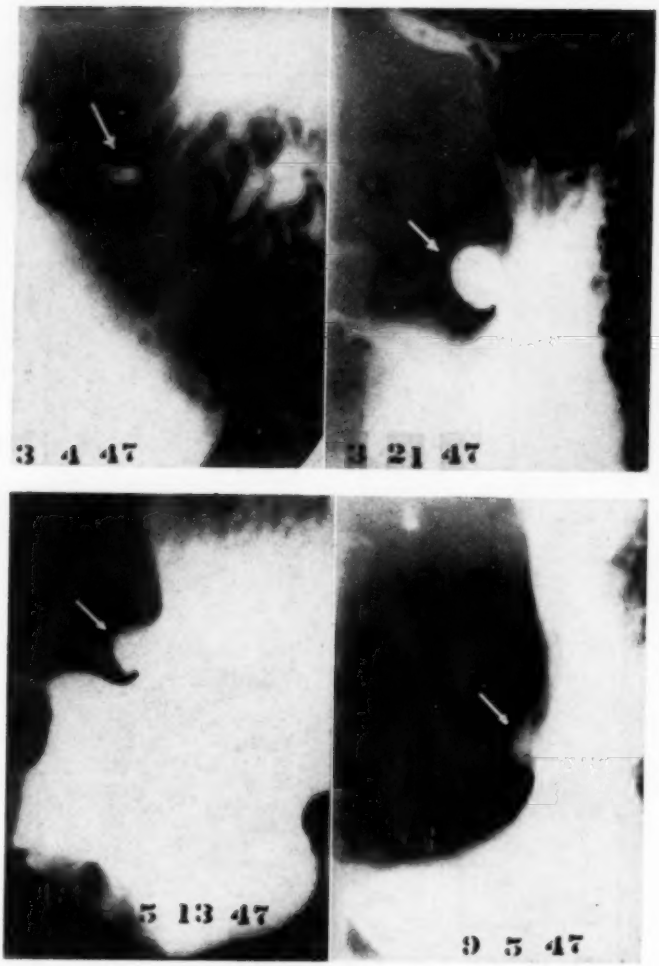

FIG. 4. E. F. Intractable gastric ulcer. The failure to heal by May 13 attributable to inadequate neutralization of the gastric acidity and impaired gastric emptying, constituted an indication for surgery without further delay; the persistence of the ulcer for four more months of medical management provides further support for this view.

INTRACTABLE DUODENAL ULCER

In duodenal ulcer, intractability can usually be correlated with hypersecretion and stenosis. The average secretory rate in terms of the 12-hour nocturnal fasting secretion is approximately four times the average normal; in many individuals it is six or eight times the normal.[4] In these patients

it is difficult to neutralize the acid completely during the day and practically impossible to do so during the night except for brief periods of time.[5] The conventional methods of therapy may afford only temporary relief. One should bear in mind, however, that patience and perseverance are, for both the patient and the physician, essential components of any therapeutic program. We have found radiation therapy directed at the fundus of the stomach to be helpful in many such patients. Unfortunately, the amount of radiation which can be given safely is limited and the effect is extremely variable. Occasionally dramatic results are obtained.[6, 7]

A physiologist, 33 years of age, first seen in January, 1945, gave a history of periodic epigastric distress of three-and-a-half years' duration. A massive hemorrhage had occurred a year before admission. The pain for several weeks prior to entry had been very severe, almost continuous day and night. Roentgen-ray examination disclosed a large central crater in the duodenal bulb with moderate deformity.

FIG. 5. W. B. Prolonged reduction of gastric secretion following radiation therapy.[8]

The standard hourly antacid program of the Sippy type was instituted, with complete relief of the pain. Radiation therapy was administered to the fundus and body of the stomach, a depth dose of 1,650 r. in 12 treatment days. The acid secretion during the night was abolished for at least three months; the response to histamine was markedly depressed for seven months (figure 5). Except for a very transitory disturbance associated with the severe illness of his wife five years ago, the patient has remained well.

A woman, now 63 years of age, first experienced epigastric distress of the ulcer type in 1930; it recurred periodically in spite of medical management. A posterior gastroenterostomy was performed in 1933. In 1936, because of recurrent pain and hemorrhage, the gastroenterostomy was undone, a jejunal ulcer being excised. The original epigastric pain recurred in 1937. Ulcer management was resumed; in addi-

tion, the patient received a course of radiation therapy which produced a histamine anacidity of approximately six months' duration. The acid then returned, but in the succeeding 10 years the response to histamine stimulation did not reach the pre-radiation level. There has been no distress (figure 6).

In these two patients the addition of radiation therapy to the therapeutic program seemed to be responsible for the favorable results obtained. The prolonged periods of post-radiation histamine achlorhydria are noteworthy. Unfortunately, secretory depressions of this magnitude cannot be obtained regularly or even frequently.

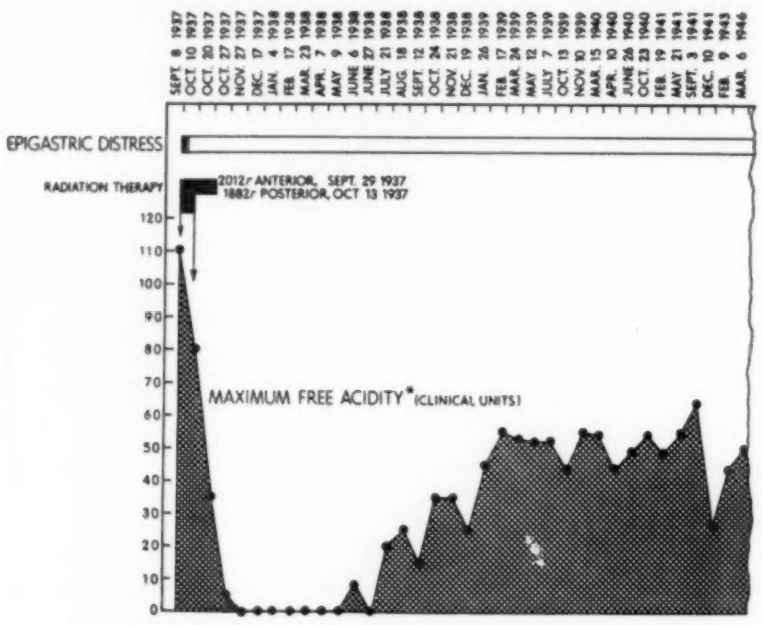

FIG. 6. G. W. Intractable duodenal ulcer—no recurrence following radiation therapy in 1937 with prolonged secretory depression.[7]

In recent years Dr. Dragstedt has shown that complete vagotomy abolishes the gastric hypersecretion. The average total 12-hour fasting night secretion of hydrochloric acid in a group of patients with duodenal ulcer was reduced from 1,904 mg. to 417 mg. after vagotomy [9]; this compares with an average value in normal individuals of 661 mg.[1] Thus, vagotomy provides another approach to the problem of intractable duodenal ulcer. In our experience, the patients in whom this operation is to be considered are usually ones with stenosis as well as hypersecretion. For this reason, and also because a successful vagotomy decreases gastric motility as well as secretion, a

posterior gastroenterostomy should be performed along with the transabdominal vagotomy. Thus far, the results of this operation have seemed to us to be more satisfactory than the more radical and more mutilating operation of subtotal gastrectomy. The following case is illustrative:

A male photoengraver, now 53 years of age, developed severe upper abdominal pain in January, 1940; an exploratory operation a few months later was reported to have disclosed inoperable cancer of the pancreas. In February, 1941 a duodenal ulcer was demonstrated by roentgen-ray; the severe pain was relieved by intensive antacid management and by radiation therapy. The ulcer healed and did not recur until November, 1943. Additional radiation therapy and continued medical management gave only temporary relief. A transthoracic vagotomy in May, 1944 abolished the hypersecretion; the 12-hour secretion on two nights before operation was 2,319 and 2,839 mg. of hydrochloric acid; two months later the value was 1,028 mg. Because of retention resulting from the stenosis and the impairment of motility, a posterior gastroenterostomy was performed two months later. The patient has gained 75 lbs. in weight and has had no recurrence of symptoms in the intervening period of almost six years.

The incidence of recurrent ulcer following this procedure is not yet known. Certainly some ulcers will develop, for a physiologic vagotomy does not always result from what seems to be complete anatomic vagotomy. The explanation of this discrepancy is not entirely clear, nor is the frequency of its occurrence established as yet. Furthermore, the vagotomized stomach with a negative insulin test still secretes some acid; peptic activity is present, and thus ulcers may form. The so-called side effects of vagotomy, such as bloating, abdominal distention and diarrhea, have been, on the whole, less troublesome than those observed following subtotal gastrectomy. In our experience, attempts to produce a so-called medical or pharmacologic vagotomy have all been unsuccessful.

Intractable Jejunal Ulcer

Jejunal ulcers are, in a sense, all intractable. They develop, as a rule, subsequent to a posterior gastroenterostomy or subtotal gastrectomy performed for duodenal ulcer; they are rare following such procedures for gastric ulcer or in a normal stomach. Hence the secretory pattern is that characteristic of duodenal ulcer. It is reasonable to conclude that the hypersecretion is responsible for the ulcer. Therapeutically, vagotomy, if complete, is the best procedure yet devised.

A patient, now 41 years of age, developed ulcer distress in 1936. In 1943, because of continued pain and obstruction, a subtotal gastrectomy was performed. Ten months later an enormous jejunal ulcer was demonstrated by roentgen-ray. Following medical management, including radiation therapy, the ulcer healed, but a year later it recurred. A transthoracic vagotomy was performed in March, 1945, following which the ulcer healed and the patient made a rapid gain in weight. There has been no recurrence in the ensuing five years.

Recurring Massive Hemorrhage

Recurrent bleeding may be a serious manifestation of peptic ulcer; for this reason it is mentioned separately. Usually acute hemorrhage can be handled in the customary medical manner; occasionally emergency surgery is indicated. If operation is performed, the bleeding vessel should be ligated; a subtotal gastrectomy is usually the most feasible accompanying procedure. If the primary site is a duodenal or jejunal ulcer, vagotomy should be considered in addition to the resection because of the high secretory rate characteristic of these lesions. There are occasional patients in whom subtotal gastrectomy is indicated because of recurring hemorrhage.

Summary

In this paper we have attempted to present various causes of intractability in the treatment of peptic ulcer and have suggested procedures to be used under differing conditions. The differentiation between intractable patients and intractable ulcers is most important. The "intractability" of the patient is, to a considerable extent, dependent upon the patience, perseverance and skill of the physician himself. Intractable ulcers should be demonstrated by objective methods, i.e., roentgen-ray, and, in gastric ulcer, by gastroscopy also. In gastric ulcer, the possibility of cancer (peptic ulceration in carcinoma) must ever be borne in mind. For this and other reasons, resection is usually the best procedure for treatment of intractable gastric ulcer. In duodenal ulcer, careful medical management, with attention to diet, rest, antacid therapy, and nervous factors, is usually effective. In our experience, the addition of radiation therapy to the medical program has frequently proved to be of great value. True intractability is related to inability to control the hypersecretion of acid gastric juice. Vagotomy is an excellent operation in such patients for, when it is successful, it does reduce the secretory rate. Usually it should be combined with a posterior gastroenterostomy. Vagotomy is certainly the treatment of choice for jejunal ulcer. When medical management, radiation therapy and vagotomy all fail, and ulcer is definitely present, further gastric resection is the only alternative available. Ulcers do not recur after total gastrectomy! Fortunately, such a radical treatment is almost never necessary.

Conclusions

The treatment of patients with peptic ulcer is still an individual problem. Patients differ, ulcers differ, the complications vary, but the fundamental principles remain unchanged. Schwartz was correct [10] in the dictum "no acid—no ulcer." A satisfactory method for controlling the acid gastric secretion has not yet been found. Nevertheless, judicious use of the available medical and surgical procedures should result in control of both the patient and the disease.

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BRAIN ABSCESS AND CONGENITAL HEART DISEASE *

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There is a sparsity of reports in the medical literature concerning the syndrome of brain abscess and congenital heart disease. This has led to a general belief that cerebral suppuration is a relatively uncommon complication in persons with congenital cardiovascular anomalies. At the present time the literature contains reports of 28 instances of this syndrome which have been studied at necropsy and which had no evidence of bacterial endocarditis. These have been well summarized by several authors.[1, 2, 3] Two other cases with bacterial endocarditis have also been reported.[1, 4] There have been three cases representing brain abscess in persons with congenital heart disease in which there was surgical confirmation of the cerebral abscess.[5, 6] Two of these subsequently died and autopsies were not performed.[5]

Hanna, Gates, et al., and Robbins reported that in between 3.5 and 6.0 per cent of all fatal cases of congenital anomalies of the heart and great vessels this syndrome is present.[1, 2, 3] The total from which these percentages were derived included stillborn infants and cases with cardiovascular anomalies which would not predispose to the development of brain abscess. It would appear, therefore, that the incidence of cerebral suppuration in certain types of fatal congenital heart disease should exceed the percentages given above. The cardiovascular lesions which have been reported in association with cerebral abscess are the tetralogy of Fallot, Eisenmenger's complex, auricular septal defects, ventricular septal defects, and a rudimentary right ventricle with both auricles emptying into the left ventricle.[1] The auricular and ventricular septal defects were associated in many instances.

The present study was undertaken in order to determine the incidence of brain abscess in fatal cases with these various types of cardiovascular defects. Between the years of 1938 and 1947 there were 13,883 autopsies performed at Los Angeles County Hospital. Two hundred nine of these had congenital heart lesions of the types under study. These cases represented all congenital anomalies, except for patent ductus arteriosus, with a potential anatomical shunt between the systemic venous and arterial tree. One hundred twenty-eight of the 209 cases were under the age of two years at the time of death. Only one instance of brain abscess occurred in this age group, and it was secondary to an otitis media. Eighty-one of the 209 cases were two years of age or older at the time of death. In this

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Since this paper was submitted for publication there has appeared an excellent summary of the literature with the presentation of two other cases of brain abscesses associated with congenital heart disease (Sancetta, S. M. and Zimmerman, H. A.: Circulation 1: 593, 1950).

latter group there were 14 instances where a brain abscess unassociated with bacterial endocarditis was found at necropsy. The incidence of cerebral suppuration for this group becomes especially significant if it is presented for each of the various types of heart lesions.

Auricular septal defects without other associated congenital cardiovascular defects represented 59 of these 81 cases which were two years of age or older at the time of death. Only three instances of brain abscesses were found at autopsy. In two of these three cases the functional state of the auricular septal defect was questionable, since in each instance the defect consisted of a foramen ovale which was well covered by a valve-like membrane. The third case had severe bronchiectasis, lung abscess, and empyema, which would serve as an excellent primary source for a brain abscess. Therefore, in none of these three cases could the cerebral abscess be accepted as an indirect result of congenital cardiac defect.

Eleven of the 81 cases had an isolated ventricular defect. Four patients in this group died as the result of a brain abscess.

The remaining 11 cases represented those with multiple congenital cardiovascular shunts. The tetralogy of Fallot was present in five of these 11 cases, and four of these five patients died as the result of a brain abscess. Three of the 11 cases had associated auricular and ventricular septal defects. Two of these three cases had necropsy evidence of brain abscess. A rudimentary right ventricle with both auricles emptying into the left ventricle and an auricular septal defect was present in two instances, and in one of these a brain abscess was the cause of death. The remaining case in this group had transposition of the great vessels and a ventricular septal defect. There was no cerebral abscess found at necropsy.

Discussion

The cause of brain abscesses which occur in the presence of congenital cardiovascular anomalies without associated bacterial endocarditis is not known. It is obvious that venous blood which is recirculated through the systemic circulation without first passing through the lungs is not subjected to the filtering action of the pulmonary capillaries. This lack of filtering has been suggested as a cause for the cerebral suppuration which may be associated with congenital heart disease.[1, 2, 3] The frequency with which brain abscesses follow a suppurative process within the lung supports the contention that the pulmonary capillaries act as a bacterial filter. On the other hand, the rather frequent occurrence of bacterial endocarditis of the aortic or mitral valves which follows oral surgery indicates that bacteria do pass through the pulmonary capillaries. It would not be expected that these bacteria could travel against the arterial blood stream and come to rest upon these valves. The rather high incidence of brain abscesses in the group with multiple cardiovascular defects certainly does suggest that this shunting of blood into the systemic arterial vessels without the benefit of the filtering action of the pulmonary capillaries plays an important rôle in

the etiology of these abscesses. It has been demonstrated experimentally in animals that the introduction of bacteria into normal brain tissue will not result in abscess formation. Previous injury to the cerebral tissue is required before suppuration will develop.[7] It is feasible that small septic emboli may be shunted from the systemic venous to the systemic arterial circulation in persons with some types of congenital heart disease. These emboli may result in damage to the cerebral tissue and resultant abscess formation. This has previously been suggested as an explanation for the development of brain abscesses in these people.[1, 2]

The fact that other tissues fail to show abscess formation suggests that the cerebral tissue has a lower resistance to bacterial invasion than does the remainder of the body. It is, of course, possible but not probable that this is true only in patients with congenital heart disease. The causative bacteria in the majority of instances of brain abscesses presented above were of low virulence. Alpha and gamma streptococci were strongly represented. It is of interest that these organisms are the ones found most commonly in the blood of normal persons following teeth extractions.[8] Therefore it would seem logical to use chemotherapy in persons with congenital heart lesions who are to have oral surgery not only to prevent subacute bacterial endocarditis but also to prevent cerebral abscess formation.

The highest incidence of cerebral suppuration was present in those cases two years of age or older at the time of death that had multiple anomalies of the cardiovascular system. Seven of the 11 cases, or 63.6 per cent, died as the result of a brain abscess. There is little doubt that a right to left shunt is present in persons with the tetralogy of Fallot.[9] The high incidence of cerebral complication in these cases may possibly be explained on this basis. In the cases with a rudimentary right ventricle, both auricles opened into the left ventricle and therefore a right to left shunt was present. The occurrence of a cerebral abscess in persons with an isolated ventricular septal defect and in patients with an auricular septal defect suggests that some blood is shunted from the right to the left side of the heart under these conditions. This has been demonstrated by cardiac catheterization in some cases of this type.[10] The overall intracardiac shunt was left to right in direction, but a right to left shunt of lesser degree may be present, especially if there is increased resistance within the pulmonary vascular tree. Cardiac decompensation was present clinically in one of the cases with an isolated ventricular septal defect that died as the result of a cerebral abscess. This case and one other with a brain abscess which was in this group showed severe pulmonary atherosclerosis at necropsy.

It is of interest to ascertain what proportion of all fatal instances of brain abscess is represented by those associated with congenital heart disease. One hundred five cases with cerebral abscess were autopsied at the Los Angeles County Hospital between the years of 1938 and 1947. The 11 acceptable cases of congenital heart disease associated with brain abscess therefore represents 10.4 per cent of this total.

The recent advent of the Blalock-Taussig operation should increase the life expectancy of persons with types of congenital heart disease characterized by recirculation of systemic venous blood through the systemic arterial vessels. Although the blood flow to the lungs is increased by the operation, the venous-arterial shunt persists. The potentialities for the development of cerebral abscesses will therefore still be present. The disappearance of polycythemia should, however, decrease the possibility for thrombus formation, and this may decrease the chance of paradoxical embolism. Gates et al.[5] emphasized that the abscesses encountered in these

TABLE I

Age in Years	Sex	Pathology File Number	Clinical Diagnosis	Heart Lesion	Size of Abscess	Location of Abscess
26	Male	22645	Brain abscess; rheumatic heart disease	Tetralogy of Fallot	4.8×4.3 cm.	Right temporal lobe
18*	Female	22789	Meningitis, type undetermined	I.V. septal defect	—	Left side of thalamus, subthalamus and tegmental portion of the brain stem
3*	Male	24777	Polioencephalitis; congenital heart disease; cerebral embolism	Tetralogy of Fallot	10×6.2 cm.	Left parietal lobe
6†	Female	27604	Peritonitis; ruptured appendix	Tetralogy of Fallot	2×3 cm.	Left frontal lobe
28	Female	28849	Brain abscess	Two I.V. septal defects	Small	Cortical region of the left occipital lobe
30	Female	31177	Subarachnoid hemorrhage	I.V. septal defect	3.3×2.0 cm.	Right temporal lobe
16	Male	32952	Bacterial endocarditis; purulent meningitis	I.V. and I.A. septal defects	3.5×2.0 cm.	Right occipital lobe
56	Female	33215	Meningitis	I.V. septal defect	Large	Right temporal, parietal and occipital lobe
6	Male	33661	Meningitis; congenital heart disease	Absence of I.A. septum, I.V. septal defect, rudimentary right ventricle, am. pulmonary artery	2.3×3.0 cm. and 1.2×3.0 cm.	Right frontal lobe Left frontal lobe
13	Male	34277	Deferred; congenital heart disease	I.A. and I.V. septal defects	—	Centrum of right parietal lobe and anterior portion of the right occipital lobe
6	Female	35733	Meningitis; tetralogy of Fallot	Tetralogy of Fallot	2×3 cm.	Left frontal lobe. Smaller abscesses in both parietal lobes

* Previously reported by Hanna.

† This case developed the brain abscess during her post-operative course following an appendectomy.

cases are usually solitary and amenable to surgical drainage. The antemortem diagnosis of this syndrome is not correct in the majority of the cases. At the present time there is only one report of a surgical cure of a brain abscess which developed in a person with congenital heart disease.[6]

Nine of the 11 cases reported in this paper which represent the syndrome of cerebral abscess and congenital heart disease have not been previously recorded. The accompanying table (table 1) summarizes the pertinent data of these cases. It should be noted that most of the brain abscesses developed after the second decade of life. The mean age at death of these patients was 19.6 years.

Summary

1. The autopsy incidence of brain abscesses associated with congenital cardiovascular shunts, not including patent ductus arteriosus, was studied.

2. There were 11 acceptable examples of this syndrome found in a series of 13,883 autopsies which were performed at the Los Angeles County Hospital between the years of 1938 and 1947.

3. These 11 cases were over two years of age at the time of death. There were 81 cases in this same age group with autopsy evidence of the cardiovascular shunts under study.

4. The distribution of the cerebral abscesses is as follows:

   a. Four of five fatal cases with the tetralogy of Fallot.
   b. Two of three fatal cases with associated ventricular and auricular septal defects.
   c. One of two fatal cases with ventricular and auricular septal defects associated with a rudimentary right ventricle.
   d. Four of 11 fatal cases with an isolated ventricular septal defect.

5. Nine previously unreported cases of brain abscesses associated with congenital heart disease are recorded.

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SOME PROBLEMS OF POTASSIUM METABOLISM *

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THE demonstration in recent years that deficiency in intracellular potassium results in severe metabolic abnormalities, and that its repair is associated with a return to normal metabolic activity, has directed our attention to a study of factors which are responsible for the high intracellular-extracellular potassium gradient.

The basic problems of cellular potassium metabolism are immediately apparent if one considers the simple system of a human red cell suspended in plasma. The red cell contains nearly 150 mEq. of potassium per kilogram of water while the plasma contains less than 5 mEq. of potassium per kilogram of water. The questions which arise are: first, does the cellular potassium exchange with the plasma potassium; second, if it does, at what rate does this exchange occur; and third, what is the mechanism responsible for this exchange?

By means of an in vitro system which maintains human erythrocytes in an apparently normal condition for over 48 hours, and by using radioactive potassium as a tracer, it has been possible to answer the first two of these questions, as they apply to the human red cell, and to make some interesting obervations concerning the third.[1] At the onset of a typical experiment the radioactive potassium was added to the plasma. During the course of several hours the specific activity of the plasma potassium fell, and the specific activity of the cellular potassium rose, until they became equal. This demonstrates that the potassium of the red cell is constantly being exchanged with the potassium of the plasma, and it also shows that all of the red cell potassium is exchangeable.

From this and similar experiments it has been calculated that 1.6 per cent of the potassium of the human red cell exchanges per hour; or, in a system containing a liter of red cells, 1.5 mM. of potassium will cross the cell membranes in each direction every hour. The red cell exchanges potassium at a relatively slow rate. Cells of other tissues have been shown by other investigators to exchange their potassium with greater rapidity.[2] Indeed, the equilibrium in the body between the cellular potassium and the extracellular potassium is actually the resultant of a constant dynamic interchange of potassium between the two compartments. It is remarkable that

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disturbances of potassium metabolism are not more prevalent, for any impairment of the mechanism responsible for this equilibrium will result in an immediate change in the concentration of potassium in the cells and in the plasma. It is this mechanism of exchange of potassium which requires further elucidation.

In order for potassium to pass from the plasma, where it exists in a low concentration, into the cell, where it is present in a high concentration, energy must be expended. There is considerable evidence that this energy is derived from the metabolism of glucose, and that the metabolism of glucose and the metabolism of potassium are closely related. Human erythrocytes utilize one millimol of glucose for each millimol of potassium that enters the cells. The temperature coefficients of the rate of transfer of potassium and of the rate of utilization of glucose by human erythrocytes are identical.[1] Red cells lose potassium if their supply of glucose is exhausted.[2] At first this is apparently due to an increase in the amount of potassium leaving the cell. With the passage of time, however, the amount of potassium entering the cell becomes reduced.[4]

It appears not only that glucose is necessary for the cellular metabolism of potassium, but also that potassium is necessary for the cellular metabolism of glucose. Buchanan, Hastings, and Nesbett demonstrated that liver slices incubated in a medium containing potassium in a high cellular concentration (130 mM./L.) form more glycogen than do liver slices incubated in a medium containing a low potassium concentration such as one finds in plasma.[5] It has also been shown by other investigators that potassium is specifically required for some enzymatically controlled reactions in the carbohydrate cycle.[6] Furthermore, it has been demonstrated that following the administration of insulin to experimental animals there is a decrease in the serum potassium level.[7] The fact that this potassium shift is indeed associated with the augmented carbohydrate metabolism is substantiated by the recent in vitro experiments of Kamminga, Willebrands, Groen, and Blickman on rat diaphragm muscle.[8] They found that if insulin is present, more potassium moves into the muscle cells. At the same time, when insulin is present, more glucose is utilized by the cells.

With this chain of evidence derived from observations on biochemical reactions, and in vivo and in vitro experiments, the intimate relationship between potassium and carbohydrate metabolism seems to be well established. It is not known, however, if the two are directly linked through the formation of a potassium salt of a phosphorylated carbohydrate intermediate,[9] or whether the metabolism of glucose may provide energy by supplying high energy phosphate bonds to a reaction which directly controls the transfer of potassium. The latter is more in keeping with the present views on energy transformations in biological systems.

There are certain observations which suggest that, by means of this energy transfer mechanism, potassium metabolism may be related to another series of chemical reactions, namely, those involving acetylcholine metabo-

lism. Nachmansohn has concluded that the permeability of nerve membranes to ions is increased by the action of acetylcholine.[10] Fenn and Gerschman have recently shown that isolated frog nerve will lose more potassium when it is exposed to acetylcholine.[11] Greig and Holland have demonstrated an increased permeability of dog erythrocytes in the presence of choline esterase inhibitors.[12]

Human red cells lose potassium when incubated in the presence of high concentrations of choline esterase inhibitors.[4] Physostigmine, which is a reversible choline esterase inhibitor, and diisopropyl fluorophosphate, which is an irreversible choline esterase inhibitor, both cause potassium to leak out of erythrocytes. Not only is the inhibition of the breakdown of acetylcholine possibly related to cellular potassium metabolism, but so also is the inhibition of the formation of acetylcholine. Acetylcholine formation in nerve is catalyzed by the enzyme choline acetylase. 2-methyl-1,4-naphthoquinone and methylene blue are reported to be inhibitors of choline acetylase.[13] They also cause potassium to leak out of red cells.

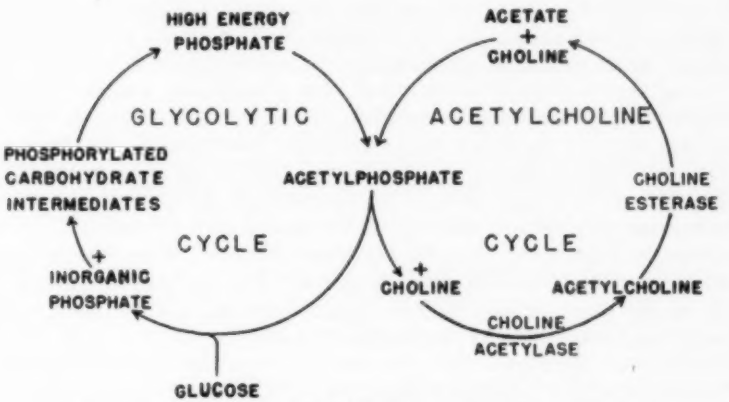

FIG. 1. The interrelation of carbohydrate and acetylcholine metabolism.

It would seem from this evidence, and from that presented by Nachmansohn and others, that the cellular metabolism of potassium may be closely associated with the cellular metabolism of acetylcholine. A theoretical scheme linking the carbohydrate cycle to the acetylcholine cycle is shown in figure 1. The metabolism of glucose yields high energy phosphate bonds which, through the intermediation of acetylphosphate, may participate in the synthesis of acetylcholine. In this series of reactions it is only necessary to supply glucose continually. The other participants undergo reutilization. The importance of the potassium ion concentration in the reactions of the carbohydrate cycle has been mentioned. The work of Torda and Wolff [14] and of Nachmansohn [15] indicates that the potassium ion concentra-

tion is also of importance in controlling the rates of formation and breakdown of acetylcholine. It is possible not only that the cellular potassium ion concentration may control the rates of these reactions, but also that these reactions may control the cellular potassium ion concentration.

In the in vitro system used, apparent interference with this chain of reactions at one or more of the following three points causes alterations in cellular potassium metabolism: first, glucose metabolism; second, acetylcholine formation; and third, acetylcholine breakdown. There is much information suggesting that certain clinical disorders of potassium metabolism may be in part the result of similar interferences. For example, the association of derangements of carbohydrate metabolism with alterations in potassium metabolism is well known. A deficiency of insulin, with resultant diabetic acidosis, is accompanied by a loss of intracellular potassium.[16] The converse of this is seen following the administration of insulin either to the person with diabetes or to the normal individual, when potassium moves from the extracellular compartment to the intracellular compartment, and low serum potassium levels are found. During the treatment of diabetic acidosis, when in addition the intracellular and extracellular water content is being increased to normal, the potassium deficiency may become so pronounced that muscular paralysis results.[17] An effect similar to that seen following insulin administration is seen after epinephrine, which also causes alterations in carbohydrate metabolism.[18] Following epinephrine, after a very transient rise, there is a fall in the serum potassium.[19]

It is of interest that in patients having familial periodic paralysis, attacks of paralysis may be induced by either insulin or epinephrine, both of which cause potassium to move from the plasma into the cells.[20] During spontaneous attacks of paralysis, potassium likewise moves into the cells from the plasma. There is evidence that this disorder may be related not only to alterations in carbohydrate metabolism but also to acetylcholine metabolism, because attacks of paralysis may be relieved not only by the administration of potassium salts but also by acetylcholine-like compounds, such as mecholyl.[21] Certain observations concerning myasthenia gravis, in which the paralysis can be relieved by choline esterase inhibitors, suggest that possibly it also might be considered as a disorder of cellular potassium metabolism on the basis of the theoretical scheme which has been discussed.

The diversity of clinical conditions which appear to be associated with derangements in the metabolism of potassium reflects the importance of this element in the normal functioning of cells. Much more information about the exact rôle that potassium plays in cellular reactions is needed in order to provide answers to the many problems of potassium metabolism.

Summary

An in vitro red cell system has been used to determine the rate of exchange of potassium between human erythrocytes and plasma. All of the

red cell potassium is free to exchange, and this exchange takes place at a constant rate. There is a constant dynamic interchange of potassium between the intracellular and the extracellular compartments. In the human red cell the maintenance of the potassium concentration gradient is dependent on glucose metabolism. Substances which apparently interfere with glucose metabolism, acetylcholine synthesis, and acetylcholine breakdown will also interfere with the maintenance of the cellular potassium concentration gradient. The possible relationship of these observations to certain clinical problems of potassium metabolism has been indicated.

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THE EFFECTS OF DIBENAMINE ON SEVERE HYPERTENSION *

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The well known rôle of the sympathetic nervous system in hypertension has led to search for sympatholytic drugs for therapeutic purposes. An extensive study of the sympatholytic agent, N-N-dibenzyl-β-chlorethylamine (Dibenamine †) in experimental animals has revealed the following pharmacological effects:[1, 2, 3, 4, 5, 6, 7, 8] (1) blockade of the usual pressor response to epinephrine and replacement by a depressor response; (2) prevention of ventricular tachycardia and fibrillation, ordinarily produced by toxic doses of epinephrine in dogs; (3) production of miosis and extension of the nictitating membrane in cats; (4) reduction of experimentally induced renal hypertension in rats and dogs; and (5) prevention of anti-curare action of epinephrine in dogs.

Dibenamine does not directly inactivate epinephrine but rather blocks its excitatory action (Sympathin E) at the effector cell, with consequent unmasking of inhibitory responses (Sympathin I).[2] After therapeutic doses of Dibenamine, smooth muscle contraction may still be elicited by agents which act directly, such as angiotonin and pituitrin.[9, 10, 11]

Toxic reactions in animals consisted of: (1) local tissue damage, and (2) stimulation of the nervous system, ranging from irritability to generalized convulsions. Cerebral excitatory action was decreased by slowing the rate of administration and by pretreatment with barbiturates. The lethal dose greatly exceeded the effective blocking dose, and only slight cumulative toxicity was observed which subsided upon withdrawal of the drug. Although Dibenamine is related chemically to the nitrogen mustards, it failed to depress bone marrow activity.

Hecht and Anderson [12] studied the pharmacologic effects of intravenously injected Dibenamine in 20 normotensive subjects and demonstrated: (1) slight drops in supine systolic and diastolic pressures in five of the total; (2) definite orthostatic hypotension in all subjects; and (3) marked pupillary constriction. They administered Dibenamine to 10 patients with hypertension and found a moderate fall in supine pressures in two cases. They also demonstrated increased peripheral blood flow in patients with peripheral vascular disease. In spite of the toxic reactions and the disappointing results in their small group of hypertensive patients, Hecht and Anderson

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† Trade mark of Givauden-Delawanna, Inc., New York, N. Y. Supplied through the courtesy of Dr. W. S. Gump.

intimated that the therapeutic implications of the drug had not been exhausted.

More recently, Haimovici and Medinets [13] gave Dibenamine intravenously in average doses of 5 mg./Kg. to 18 patients with normal blood pressures; to six with purely systolic hypertension; to seven with "benign" essential hypertension, and to seven with "malignant" essential hypertension. They noted orthostatic hypotension in the entire group, but found no significant lowering of supine pressure in the normotensive patients nor in those with purely systolic hypertension. A marked reduction in both systolic and diastolic pressures was observed in the patients with "benign" essential hypertension, but only a slight to moderate fall, regarded as insignificant by the authors, was found in the patients in the "malignant" phase.

When Dibenamine became available to us, a study of its effects on severe hypertensive patients was undertaken. The study was divided into two parts: (1) the intravenous administration of Dibenamine, and (2) oral administration of Dibenamine to ambulatory as well as to hospitalized patients. Although both phases of the study are still in progress, the symptomatic effects of intravenous Dibenamine in hypertensive encephalopathy, in contrast to results of other workers,[12, 13] were sufficiently encouraging to justify a preliminary report.

Procedure in Intravenous Administration of Dibenamine

I. *Selection of Cases.* Patients with severe hypertension were placed at bed rest with barbiturate sedation for seven days or more, except in Case 2, where the control period was only six days. If the blood pressure fell below 200/110 mm. Hg the patient was eliminated from the study. Other contraindications to treatment included: recent or old myocardial infarction, cardiac failure, severe anemia, leukopenia, evident hepatic damage, or intercurrent acute diseases.

The final group selected for intravenous injections of Dibenamine totaled 14. Of these, 10 patients (Cases 1, 2, 3, 4, 5, 6, 7, 9, 10, and 13) were in the "malignant" phase of hypertension as judged by typical clinical manifestations of hypertensive encephalopathy and hypertensive retinopathy of grades three to four. Three of these 10 patients had underlying chronic glomerulonephritis. Two patients were in frank uremia, and all but one of the remainder had blood urea levels above 35 mg. per cent.

The remaining four patients (Cases 8, 11, 12, and 14) were classified as severe "benign" hypertensives. Their blood pressures had been maintained on a plateau above 200/110 during the control period, but on the first day of treatment, preceding administration of Dibenamine, pressures below 200/110 were recorded in two of this group (Cases 8 and 14).

II. *Method of Study.* Prior to administration of Dibenamine the following studies were made: (1) registration of blood pressure twice daily during seven to 10 days of bed rest; (2) frequent urinalyses; (3) a minimum

of two determinations of blood urea and one or more urea clearance tests; (4) electrocardiogram; (5) cardiac roentgenogram; (6) bromsulfalein test; (7) intravenous or retrograde pyelogram; and (8) complete blood count. In nine of the cases the response to tetraethylammonium chloride (Etamon) was also determined.[14]

During the intravenous administration of Dibenamine, blood pressures, pulse rates and pupil size were recorded. These were recorded every 10 minutes while marked fluctuations were found; then every hour until evidence of stabilization was obtained, and thereafter at frequent intervals. Electrocardiograms were taken at the time of maximal blood pressure fall, on the day following treatment, and weekly thereafter. Urinalyses were done every other day, and complete blood count and blood urea were checked every three days following treatment. In some cases renal function was investigated by measuring the urinary volume and urea clearance immediately before, during and immediately after treatment. The fundi were reëxamined during depression of blood pressure and daily thereafter. The cardiac roentgenograms, bromsulfalein test and blood urea were repeated at the close of the observation period. Patients were observed in the hospital for from one to several weeks after therapy.

III. *Dosage.* The Dibenamine hydrochloride solution was administered intravenously in an infusion of 5 per cent glucose in distilled water. After the infusion was flowing freely the desired amount of Dibenamine solution was added to the contents of the flask and mixed thoroughly. The rate of flow was then adjusted so that the fluid was administered over a period of not less than 45 to 60 minutes. The initial dose of Dibenamine ranged from 2 to 5 mg./Kg. of body weight. Subsequent doses were dependent upon therapeutic response and toxic reactions, but were usually increased to a range of 5 to 8 mg./Kg. and reached a maximum of 10 mg./Kg. in one case. The injections were repeated at two to three day intervals in some cases; the patient in Case 3 received 6 mg./Kg. daily for six consecutive days. A total of 39 courses of intravenous Dibenamine was given during the study.

Results of Intravenous Administration

I. *Pupils.* Pupillary constriction was noted in all patients and was usually the first evidence of Dibenamine action. The time of onset of constriction after starting the injection varied from 10 to 60 minutes and averaged 27 minutes. Maximal constriction was observed at an average time of 62 minutes. Homatropine was instilled into one eye of some of the patients and pupillary constriction was observed parallel to that in the opposite (control) eye.

II. *Effects on Blood Pressure.* Table 1 summarizes the observations on blood pressures taken in the supine position. The blood pressure began to fall within 60 minutes in all but five of the 39 injections, and reached its nadir in an average period of two and one half hours. When the maximum

TABLE I

Blood Pressure Response Following Intravenous Dibenamine

Case No.	Dosage mg./Kg.	Basal B. P.	Lowest B. P.	Time of Lowest B. P. in Min.	Duration of B. P. Fall in Hours	Fall of B. P.	Maximal Fall in B. P.
1	4	208/108	178/80	60	24	30/28	30/28
2	5	210/178	152/114	110	48	58/64	
	6	196/166	186/124	150	18	10/42	
	6	206/158	190/60	210	(19 days)*	16/98	
	6	242/170	200/124	50	6	42/46	
	8	226/164	170/116	(18 hours)*	(19 days)*	56/48	
	8	224/170	176/128	110	48	48/42	
	10	236/188	160/130	240	(31 days)*	76/58	76/58
3	4	220/144	164/118	300	18	66/26	
	6	218/140	186/124	(24 hours)*	48	32/16	
	8	204/138	140/104	360	36	64/34	
	8	190/130	154/120	360	24	36/10	66/34
4	5	228/154	170/112	180	24	58/42	
	7.5	228/158	190/128	360	48	38/30	
	9	220/148	164/120	90	48	56/28	58/42
5	4	228/156	220/156	70	1.5	8/0	
	6	240/156	160/118	60	7	80/38	
	8	230/136	212/106	120	6	18/30	80/38
6	4	218/124	160/98	100	48	56/26	
	5	226/134	162/100	80	36	64/34	
	6	204/120	160/88	(24 hours)*	36	44/32	64/34
7	3.5	210/144	104/88	90	24	106/56	
	2.5	200/138	130/98	100	6	70/40	106/56
8	2.6	160/110	120/90	30	1	40/20	
	2.6	208/138	194/108	120	7	14/30	40/20
9	4	200/140	198/140	50	1	2/0	
	6	222/150	210/126	210	7	12/24	12/24
10	5	236/170	176/116	80	5	60/54	
	6	236/166	154/110	120	24	82/56	82/56
11	5	224/160	204/140	100	5	20/20	20/20
12	5	224/130	164/94	210	48	60/36	60/36
13	6	204/134	110/80	240	48	94/54	94/54
14	5.2	190/110	138/80	180	36	52/30	52/30
Average	6			150	24½	48/37	59/38

* These results were not used in computing averages.

response of each patient was averaged, a drop of 59 mm. Hg systolic and 38 mm. Hg diastolic was found.

The duration of blood pressure depression (i.e., the time elapsing until return to pretreatment level) varied considerably in different patients, ranging from one hour in Cases 5, 8, and 9, to 48 hours or more in Cases 2, 3, 6, 8, and 12, and averaged 24.5 hours for the group.

The degree and duration of blood pressure fall could not be correlated directly with either the dosage or rate of injection. The daily administration of doses of 6 mg./Kg. for six days (to the patient in Case 3) produced no demonstrable cumulative effects nor tachyphylaxis.

The observations of Hecht and Anderson and Haimovici and Medinets on postural hypotension were confirmed. Significant orthostatic drops in blood pressure were demonstrable for as long as five to six days after the blood pressure in the supine position had returned to the pretreatment level.

III. *Comparison with Etamon.* A comparison of the hypotensive effects of Dibenamine with that of tetraethylammonium chloride (Etamon) was made in nine cases. Etamon was given intravenously in doses of 100 to 500 mg., and the Dibenamine course used for comparative purposes was

TABLE II

Comparison of Blood Pressure Effects of Etamon and Dibenamine

Case No.	Etamon		Dibenamine	
	Dosage, c.c.		Dosage mg./Kg.	
2	3.0	Basal B. P. 170/130 Min. B. P. 148/110 Diff. B. P. 22/20	6.0	Basal B. P. 206/158 Min. B. P. 190/60 Diff. B. P. 16/98
3	5.0	Basal B. P. 172/130 Min. B. P. 140/110 Diff. B. P. 32/20	8.0	Basal B. P. 190/130 Min. B. P. 154/120 Diff. B. P. 36/10
4	5.0	Basal B. P. 204/136 Min. B. P. 190/140 Diff. B. P. 14/0	5.0	Basal B. P. 228/150 Min. B. P. 170/110 Diff. B. P. 58/42
6	3.0	Basal B. P. 232/136 Min. B. P. 170/110 Diff. B. P. 62/26	5.0	Basal B. P. 226/134 Min. B. P. 162/110 Diff. B. P. 64/24
7	1.0	Basal B. P. 204/135 Min. B. P. 120/90 Diff. B. P. 64/45	3.5	Basal B. P. 210/144 Min. B. P. 104/88 Diff. B. P. 106/56
10	3.0	Basal B. P. 234/164 Min. B. P. 176/130 Diff. B. P. 68/34	6.0	Basal B. P. 236/166 Min. B. P. 154/110 Diff. B. P. 82/56
12	4.0	Basal B. P. 206/130 Min. B. P. 168/104 Diff. B. P. 38/26	5.0	Basal B. P. 224/130 Min. B. P. 164/94 Diff. B. P. 60/36
13	4.0	Basal B. P. 175/120 Min. B. P. 144/98 Diff. B. P. 31/22	6.0	Basal B. P. 204/134 Min. B. P. 110/80 Diff. B. P. 94/54
14	4.0	Basal B. P. 200/126 Min. B. P. 170/106 Diff. B. P. 30/20	5.3	Basal B. P. 204/120 Min. B. P. 138/80 Diff. B. P. 66/40
Average	3.5	Diff. B. P. 40/24	5.1	Diff. B. P. 65/46

that one in which the basal pressures most closely approximated those present before Etamon was administered.

The findings are summarized in table 2. The basal blood pressures before the administration of the two drugs were comparable in six of the cases (Cases 3, 6, 7, 10, 12, and 14). The depression in blood pressure following Dibenamine was significantly longer in duration than that following Etamon. An approximately equal drop was produced by the two agents in Cases 3 and 6, but a greater depression was produced by Dibenamine in the other four cases, perhaps due to difference in dosage.

IV. *Effects on Hypertensive Encephalopathy.* The most striking therapeutic effect consisted in the relief of symptoms of hypertensive encephalopathy, and was achieved in seven of the 10 patients. Hypertensive headache refractory to other measures was completely alleviated by Dibenamine in these seven patients. The duration of relief ranged from three days to several weeks. Distinct improvement in vision was reported by three of the patients and was accompanied by decrease in retinal edema in one and by improvement in visual fields in another. Three patients who were very irritable during the control period, despite heavy sedation, became docile and coöperative after the administration of Dibenamine.

The following two case abstracts are presented as examples of clinical response to Dibenamine:

Case Reports

Case 2. A 14 year old white school girl entered Receiving Hospital on October 19, 1946, complaining of excruciating occipital and frontal headache and repeated vomiting of three days' duration. She gave a history of frequent incapacitating sore throats over a period of several years. Headaches had begun about one year previously and had gradually increased in frequency and severity. The only history of edema was an episode of puffiness of the eyes which occurred about six months before entry and lasted a few days. At that time she noted blurring of vision, consulted an oculist, and was told she had kidney trouble. Since then there had been progressive impairment of vision. Gross hematuria was first noted one week before admission, and the urine had been consistently bloody since then.

Physical examination revealed a small, poorly developed, irritable, conscious white female who appeared acutely ill. The blood pressure was 275/215 mm. Hg. Ophthalmoscopic examination revealed pronounced edema of both optic discs continuing into the surrounding retina. There was a generalized arteriolar spasm, grade IV, and sclerosis with perivascular sheathing, grade II. There were scattered recent and old "cotton wool" patches beyond the peripapillary area and there were a number of superficial hemorrhages, both recent and old. An edematous retinal detachment was found in the superior temporal quadrant of the left eye. Cardiac size was within normal limits and there was no evidence of congestive failure. No abdominal masses were palpated. The remaining physical examination was within normal limits.

Laboratory Findings: Urinary albumin varied from 3 plus to 1 plus; specific gravity ranged from 1.001 to 1.013; innumerable red blood cells were found on admission and gradually decreased; white blood cells averaged 10 to 15 per high power field; *Aerobacter aerogenes* organisms predominated in urine cultures and nonhemolytic streptococci were also present. The blood urea was 60 mg. per cent on admission and decreased during treatment to 25 mg. per cent. The blood hemoglobin

was 9.5 gm., white blood cells were 7,050, and the Kahn was negative. The electrocardiogram was normal; retrograde and intravenous pyelograms were essentially negative. Spinal fluid pressure was 350 mm. water on admission, and varied from 250 mm. to 500 mm. during the first hospital week.

The possibility of pheochromocytoma was entertained but was considered improbable because of: (1) absence of history of the usual paroxysms and inability to provoke same by the customary maneuvers; and (2) a negative histamine test.

A diagnosis was made of an acute exacerbation of chronic glomerulonephritis, complicated by hypertension in a "malignant" phase.

The hospital course is shown graphically in charts 1 A and 1 B.

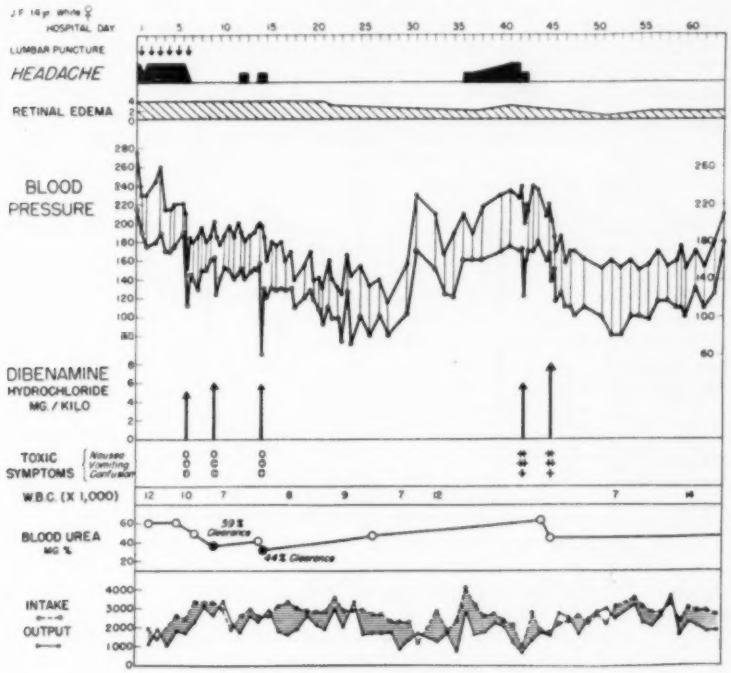

CHART 1 A. First half of hospital course of Case 2.

During the first six days of hospitalization the blood pressure became fixed in the vicinity of 220/180. Her vision and retinal edema remained unimproved and the headache continued unabated in spite of daily spinal drainages, pentobarbital in doses of 240 mg. per day, and parenteral magnesium sulfate in doses of 6 to 9 gm. per day.

Headache disappeared for the first time on the sixth day during the administration of Dibenamine in the dose of 5 mg./Kg. She was completely free of symptoms and had an average blood pressure of 190/150 for the next six days, during which a second injection of 6 mg./Kg. of Dibenamine was given. The headache then returned in a milder form but was completely relieved for a period of three weeks by a third injection of 6 mg./Kg. of Dibenamine given on the fourteenth day. The blood

pressure gradually fell after this injection and was maintained in the vicinity of 140/90 from the seventeenth to the twenty-seventh day, then slowly rose to approach admission levels between the thirty-sixth and the forty-second day. Progressively increasing headache during this period was again promptly relieved by Dibenamine, given in a dose of 6 mg./Kg. on the forty-second day and repeated in a dosage of 8 mg./Kg. on the forty-fifth day. Blood pressure stabilized in the vicinity of 160/110 for the next 17 days and then rose to admission levels between the sixty-fourth and sixty-eighth day, accompanied by return of headache. Dibenamine in a dosage of 8 mg./Kg. on the sixty-eighth day gave only transient relief, but a dose of 10 mg./Kg. on the seventy-fifth day was followed by a complete disappearance of headache and stabilization of blood pressure in the vicinity of 180/140 for the next five weeks.

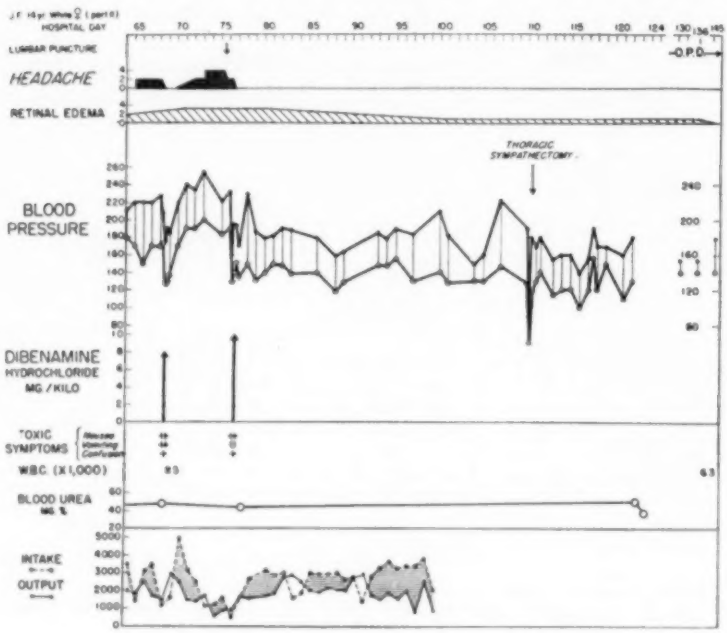

CHART 1 B. Second half of hospital course of Case 2.

The first three injections of Dibenamine caused no toxic symptoms, but the last four were accompanied by nausea, vomiting, and slight transitory mental confusion.

Each injection of Dibenamine resulted in diuresis and decrease in blood urea levels in addition to the drops in blood pressure. During the course of Dibenamine therapy, macular edema gradually disappeared and visual acuity returned sufficiently to permit the reading of fine print. The area of detached retina became reattached and papilledema eventually disappeared.

Because of the marked but temporary improvement produced by Dibenamine, thoracic sympathectomy was considered advisable and this was performed on the one hundred tenth day. Postoperative blood pressures stabilized in the vicinity of 160/120.

The patient was discharged from the hospital three weeks after operation and has been followed in the out-patient department for 15 months. The blood pressure was generally in the ranges of 160–170 to 120–140. The patient was free of headaches and blurring of vision on the last clinic visit, and is slowly gaining in height and weight.

Case 4. A 33 year old colored laborer first entered Receiving Hospital on November 27, 1946, with chief complaint of recurrent occipital headaches for one year. He gave a history of hypertension dating back seven years, recurrent ankle edema for the same period, nocturia for three years, exertional dyspnea for two years, and intermittent hematuria of four months' duration. He had suddenly lost vision in the left eye four months previously, and since then had noted gradual impairment of vision in the right eye.

Physical examination on admission revealed the following significant positive findings: The left fundus showed optic atrophy and extremely narrow "silver-wire" arterioles due to an occlusion of the central artery. Right fundus showed diffuse and focal arteriolar constriction of grade III. There was evidence of previous edema of the disc and peripapillary area, and there were several recent superficial hemorrhages. There was definite physical and roentgen evidence of left ventricular hypertrophy and pulmonary congestion. Blood pressure was 290/190.

Laboratory Findings: Twenty-four urine specimens showed specific gravities ranging from 1.003 to 1.010; constant albuminuria varying from 1 to 4 plus; occasional casts and red blood cells, and from 3 to 30 white blood cells to the high power field. Concentration test produced a maximum specific gravity of 1.014, and the total P. S. P. excretion in two hours was 20 per cent. Blood urea was 64 mg. per cent on admission and gradually fell under therapy. Urea clearance was 39.8 c.c. per minute; blood Kahn was negative; hemoglobin was 11 grams per 100 c.c.; the white blood count was 8,600 per cu. mm. The spinal fluid was under increased pressure but was otherwise normal. The electrocardiogram showed left ventricular hypertrophy. A diagnosis was made of essential vascular hypertension, "malignant" phase, with cardiac hypertrophy and hypertensive retinopathy, grade III.

The hospital course is represented in chart 2. During a 32 day control period of bed rest and sedation, the blood pressure stabilized at a level of 240/160. Severe occipital headache was present daily except for a brief period following lumbar puncture. No change was observed in vision or ophthalmoscopic findings.

Dibenamine was given in a dose of 5 mg./Kg. on the thirty-third day, following which headache disappeared for one week. The headache returned on the fortieth day and was relieved for a period of four days by an injection of 8 mg./Kg. of Dibenamine. It is noteworthy that the depression of blood pressure was transitory and limited to the 24 hour period following therapy. Moderate occipital headache was present between the forty-sixth and fifty-sixth days, at which time a third injection of 9 mg./Kg. was given. This was followed by a prolonged period of almost complete relief lasting 54 days. During this interval the blood pressure was more labile, ranging from 180–240 to 125–160. There was subjective improvement in the vision of the right eye and widening of the concentrically narrowed visual field. Definite diuresis occurred with each treatment, accompanied by a transient rise in urea clearance due to diminished tubular resorption. Toxic symptoms included nausea, vomiting, sleepiness, and moderate confusion.

Sympathectomy was refused and the patient was discharged on the seventy-ninth hospital day (i.e., the twenty-third day after the last injection of Dibenamine). He was followed in the out-patient department at one to two week intervals and was essentially symptom-free for the next four weeks. Severe occipital headaches returned on the one hundred tenth day (i.e., 54 days after the last Dibenamine injection) and increased progressively during the next three days. On the morning of the one

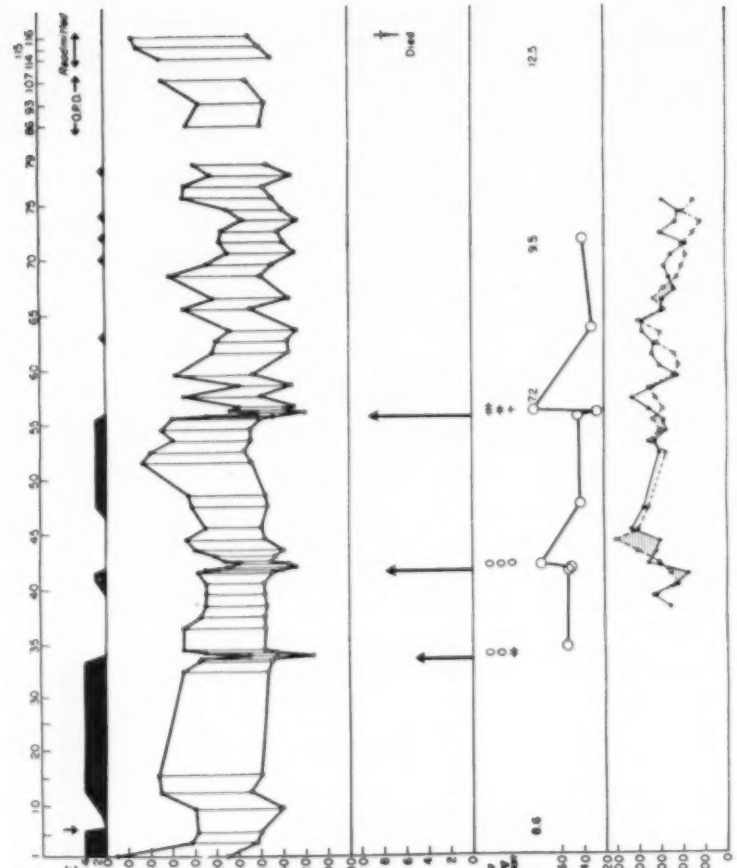

CHART 2. Hospital course of Case 4.

hundred fourteenth day he was found stuporous with marked swelling of the face, neck and upper extremities. Physical examination upon admission to the hospital showed an ecchymosis of the left eye and marked pitting edema of the face, neck and upper extremities, and slight edema of the ankles. There was pronounced bilateral chemosis. The findings were indicative of venous thrombosis extending to the superior vena cava, but the accessible deep veins could not be palpated, probably due to edema. Other physical and laboratory findings were essentially unchanged except for a blood urea of 128 mg. per cent. Skull and chest roentgen-rays contributed no additional information and the cause of venous thrombosis was not discovered. The edema progressively increased and death occurred on the third hospital day. Post-mortem examination was refused.

As is apparent from the case presentations, intravenous Dibenamine produces only a temporary remission of hypertensive headache. A major objective of Dibenamine administration was to produce sufficient improvement to permit sympathectomy. Although all 10 of the patients were considered unfit for sympathectomy on admission, a sufficiently good remission occurred in five patients to warrant recommendation of sympathectomy. A good result was obtained from Smithwick operation in Case 2, as described above. Sympathectomy was performed in one patient (Case 10), but death occurred from postoperative pulmonary atelectasis. The other three patients who were prepared for operation refused surgery; one of these (Case 4) died subsequently, the other two were asymptomatic on discharge but disappeared from observation. Two of the seven patients who responded to Dibenamine did not improve sufficiently to make sympathectomy a good risk. One of these died subsequently. The other was in poor condition at the time of discharge.

Three patients with hypertensive encephalopathy showed no improvement whatsoever in the cerebral manifestations as a result of Dibenamine. Two of these (Cases 1 and 9) were in uremic stupor prior to institution of the drug. The former died in the hospital and the latter was moribund when released to the relatives. The third patient (Case 5) had severe encephalopathy with marked mental confusion and showed no improvement in the cerebral manifestations, despite a transitory drop in blood pressure. He made an unsuccessful attempt at suicide by cutting his throat four days after the last injection of Dibenamine. He subsequently died of uremia, and autopsy revealed a severe degree of necrotizing arteriolitis in the kidneys.

V. *Renal Effects.* Records of intake and urinary output were kept in connection with 12 of the courses of Dibenamine, and a distinct diuresis was noted in 10 of these. The urinary output generally exceeded the intake on the day of treatment and often on the following day as well. The urine produced during diuresis was of low specific gravity.

In nine instances, urea clearance tests were run for three separate periods on the day of Dibenamine administration: (1) a two-hour control period immediately prior to the start of injection; (2) a period covering the administration of the drug; and (3) a two-hour period beginning immediately after the completion of therapy. In seven of the nine studies there was a

distinct increase in urea clearance during or immediately after Dibenamine administration. The change was presumably due to decreased tubular reabsorption.

VI. *Toxicity.* Toxic reactions were experienced by all alert patients. The time of appearance varied from 10 minutes to three hours after the start of therapy, and averaged 59 minutes. The advent of toxic symptoms generally preceded the fall in blood pressure. Nausea and vomiting occurred in eight of the 14 patients and in 15 of 39 injections (38 per cent of all injections); drowsiness was observed in five of the 14 patients and in 21 of 39 injections (54 per cent of all injections); restlessness or transitory mental confusion was noted in nine of the 14 patients and in 11 of 39 injections (28 per cent of all injections). The confusion was so alarming to one patient (Case 8) that she refused further treatment after the second injection.

Generalized epileptiform convulsions occurred in one patient (Case 7) with an initial dose of 3.5 mg./Kg., given in a period of 60 minutes, and recurred after a second injection of 2.5 mg./Kg., given in a period of 75 minutes. This patient showed considerable mental confusion before start of therapy and responded to the two doses in almost identical fashion. The blood pressure fell slightly between the tenth and fortieth minutes after the start of injection and then rose above the control level. Increased mental confusion accompanied the rise in pressure, and generalized epileptiform convulsions began 75 minutes after the start of each injection and lasted five to 10 minutes. The blood pressure reached a peak during the convulsion and dropped precipitously thereafter to a nadir of 108/88 in the first course and 130/98 in the second. An abrupt rebound in blood pressure then occurred, followed by a second convulsion at 100 to 110 minutes in each course. The transient increase in mental confusion disappeared after about four hours, leaving the patient distinctly clearer than before injection. Although this patient had classical hypertensive encephalopathy, manifested by several transient episodes of loss of consciousness prior to admission, and by a third epileptiform convulsion several weeks after discontinuance of Dibenamine, it is believed that the convulsion observed in connection with injections represented a toxic reaction to the drug.

Severe local tissue reaction was noted on one occasion when minimal extravasation of fluid occurred. Occasionally there were complaints of discomfort at the venipuncture site during the intravenous infusion, but no evidence of thrombophlebitis was found.

Dibenamine administration had no effect on the electrocardiogram nor on cardiac size. The hemogram was not modified by the use of Dibenamine and no change was noted in the liver function test employed. Postmortem studies were obtained on two patients (Cases 5 and 10) and revealed tissue changes compatible with essential hypertension, "malignant" phase, including nephrosclerosis with renal arteriolar necrosis. Gross and microscopic studies failed to demonstrate any changes which could be attributed to the use of Dibenamine.

Three other patients of the group are known to be deceased (Cases 1, 3, and 4), and though post mortems were not available there was no clinical evidence to indicate that Dibenamine treatment contributed to their deaths.

Procedure in Oral Administration of Dibenamine

Seventeen patients received Dibenamine by the oral route. The criteria upon which the first eight cases were selected for oral therapy were identical to those used in the selection of patients for intravenous Dibenamine. The other nine cases were ambulatory patients regularly attending the Hypertension Clinic and were chosen because of blood pressures sustained above 200/110 mm. Hg during the preceding three months of out-patient care. Weekly observation was maintained for an additional contact period of at least four to six weeks, during which phenobarbital was administered in doses of 30 mg. three times a day.

During the period when Dibenamine was given orally to hospitalized patients, blood pressure readings were taken three times daily, cold pressor tests were determined twice weekly, and toxic reactions were recorded as they occurred. Patients followed in the out-patient department had weekly recordings of blood pressure and pulse. Complete blood count and cold pressor tests were checked every two to four weeks in this group.

Dibenamine was supplied in 0.125 gm. and 0.25 gm. enteric coated tablets. The initial dose varied from 0.25 gm. once daily, given after breakfast, to 0.25 gm. three times a day, given after meals. The dosage was gradually increased by one tablet daily until either therapeutic or toxic effects resulted. The maximal dose employed was 0.5 gm. three times a day.

Results of Oral Administration

Effects on Blood Pressure. A definite drop in supine blood pressure was observed in only three of the 17 patients who received Dibenamine by the oral route. The reduction in blood pressure in these three patients was not marked, averaging 37 mm. systolic and 17 mm. diastolic. The failure to obtain better results may have been due to the limitation in the amount of Dibenamine tolerated by the oral route. Symptomatic relief of hypertensive headache occurred in two patients in whom there was no significant change in blood pressure.

A more consistent effect achieved with these doses was abolition of the immediate hyperreaction to the cold pressor test. This effect was further studied by hospitalizing some of the patients, determining the basal pressure after a week of bed rest, and then performing cold pressor tests. In five such patients, immediate elevations of 30 mm. or more in both systolic and diastolic pressure were found after immersion of the opposite hand in water at 4° C. for one minute. The test was subsequently repeated after the oral administration of 0.5 to 0.75 gm. Dibenamine (approximately 9 to 15 mg./Kg.). These amounts did not significantly alter the supine blood

pressure but abolished the hyperreaction of each patient to the cold pressor test.

Toxicity. Nausea and vomiting occurred in every patient receiving Dibenamine by the oral route. The amount necessary to produce nausea and vomiting was constant in a given patient but varied in the series from 0.125 gm. to 1.5 gm. daily. Only one of the 17 patients tolerated therapeutically effective dosage without toxic symptoms.

Rockwell [15] treated 50 patients with psychopathologic disorders with oral Dibenamine. He reported that prior atropinization significantly reduced the incidence of nausea and vomiting. We are at present investigating the efficacy of atropine and other agents in the protection against gastrointestinal irritation produced by oral Dibenamine.

Comment

The results of this preliminary study indicate that Dibenamine by the intravenous route is of value in the symptomatic relief of hypertensive encephalopathy. Because of its toxicity, Dibenamine is not the agent of first choice in hypertensive encephalopathy but should be reserved for patients failing to improve on standard methods of treatment, namely, bed rest, low sodium diet, venesection, lumbar puncture, and parenteral magnesium sulfate. To reduce the danger of severe toxic manifestations, all doses should be given by slow intravenous infusion over a period of at least one hour during which the patient is under constant medical observation. The initial dose should be restricted to 2 to 3 mg./Kg. and, if tolerated, subsequent doses should be increased to the therapeutic range of 5 to 10 mg./Kg.

The duration of blood pressure depression varied considerably in different patients and averaged twenty-four and one-half hours. Relief of headache and other symptoms of hypertensive encephalopathy was obtained in seven of the 10 cases. Although the symptomatic remission may have been initiated by the depression of blood pressure and by the diuresis that usually accompanied Dibenamine administration, it was maintained in some cases for days or weeks after the blood pressure and urinary output had returned to pretreatment levels. However, the symptomatic relief was only temporary even in the most favorable cases.

It would thus appear that Dibenamine is merely an accessory measure, to be used in an attempt to tide the patient over an acute episode of hypertensive encephalopathy and in the hope of obtaining sufficient improvement to permit sympathectomy.

It should be emphasized that intravenous Dibenamine is contraindicated in the treatment of the ambulatory hypertensive patient, not only because of its toxicity but also because of the profound and protracted orthostatic hypotension. Dibenamine by the oral route has received a preliminary trial in such cases but has not been tolerated in therapeutically effective doses because of nausea and vomiting.

Summary

1. A preliminary study of the effects of N-N-dibenzyl-β-chlorethylamine (Dibenamine), a sympathicolytic agent, has been made on patients with severe hypertension after a suitable control period on standard medical treatment.

2. Dibenamine was administered by slow intravenous drip in doses of 2 to 10 mg./Kg. in 14 patients with fixed hypertension, including 10 in the "malignant" phase. A transient depression of supine blood pressure was observed in every case, lasting from one hour to several days and averaging 24.5 hours. Upon averaging the maximal response of each patient, a drop of 59 mm. Hg in the systolic and 38 mm. Hg in the diastolic pressure was found. The depression of supine blood pressure was more prolonged in duration and usually greater in magnitude than that produced by tetraethylammonium chloride. Orthostatic hypotension was demonstrable for as long as five to six days after the supine pressure had returned to the control level. Transient miosis, diuresis, and increase in urea clearance constituted other clinical effects.

3. A temporary symptomatic remission in hypertensive encephalopathy was obtained in seven of the 10 patients in the "malignant" phase. Relief of headache lasted from three days to several weeks, and persisted in some cases after the supine blood pressure had returned to pretreatment levels.

4. The only clinical application suggested by these studies is the possible use of Dibenamine as an accessory measure in hypertensive encephalopathy in an attempt to tide the patient over an acute episode and in the hope of obtaining sufficient improvement to permit sympathectomy. Even under these circumstances, Dibenamine is not the agent of first choice because of its toxicity, but should be reserved for patients failing to improve on standard medical measures.

5. Toxic reactions were experienced by all alert patients. Restlessness and mental confusion occurred in nine patients, nausea and vomiting in eight, drowsiness in five, and generalized epileptiform convulsions in one patient.

6. Intravenous Dibenamine is contraindicated in the treatment of the ambulatory hypertensive patient, not only because of its toxicity but also because of the marked and prolonged orthostatic hypotension.

7. Enteric coated tablets of Dibenamine were administered orally to 17 patients with severe "benign" hypertension in doses of 0.25 to 0.5 gm. once to three times daily. Abolition of the immediate hyperreaction to the cold pressor test was observed in the absence of significant change in the supine blood pressure. All patients experienced nausea and vomiting, and only one tolerated the drug in therapeutically effective doses. Efforts at prevention of gastrointestinal irritation are in progress.

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A LONG-TERM STUDY OF THE NATURAL HISTORY OF ESSENTIAL HYPERTENSION *

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IT is indeed an honor to be given the opportunity to address this distinguished audience as one of the former Research Fellows of the College who have been asked by your President to report on the way in which their work has been influenced by the advantages derived from the tenure of a Research Fellowship of the American College of Physicians.

My Fellowship year, which had been postponed from 1940 to 1946 because of war service with the Royal Canadian Air Force, proved to be an ideal transition period from military to civilian research, and provided me with an excellent opportunity to resume my pre-war interest in the natural history of essential hypertension.

Having been granted the privilege of working under the joint direction of Professor Jonathan Meakins, in Medicine, and Professor Lyman Duff, in Pathology, it was only natural that my first project should have been in the field of clinicopathological correlation. My general working hypothesis in approaching the problem was the concept that the pathogenesis of essential hypertension involves a genetically determined abnormality in the contractile mechanism of arteriolar smooth muscle, rather than a derangement of the neurogenic and humoral factors which regulate this contractility. In searching for an improved method of studying the size of the lumen of arterioles, it seemed profitable to explore the potentialities of the latex injection technic which had been used extensively in Dr. Duff's laboratory.[1] As a result of my interest in this problem, the opportunity arose to review for the *American Journal of the Medical Sciences* [2] all the published data on alterations in the lumen diameter and wall thickness of the arterioles in various organs of hypertensive patients examined by autopsy or biopsy methods. The preparation of this review was complicated by the fact that very few reports could be found in which actual measurements, as opposed to qualitative gradings, were recorded. Moreover, even in those which were satisfactory from this point of view, there was seldom any accurate information on the duration of the hypertensive state in individual patients on whose tissues the measurements were made.

It was at this stage of the project that it occurred to me, as it has probably occurred to many others, that data on any phase of the natural history of hypertensive disease would be of much greater significance if the case his-

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tory of each patient included an accurate account of the date and circumstances of the transition from the normotensive to the hypertensive state. As an extensive review of the literature revealed no systematic attempt to collect a large series of cases which fulfilled this criterion, an estimate was made of the feasibility of this type of project by determining the frequency with which such well-documented cases might be expected to occur in the ordinary run of the mill admissions to a large teaching hospital. Accordingly, the second half of my Fellowship year was devoted to an analysis of the case records of all patients, regardless of service, in which a diagnosis of essential hypertension had been made during the 10 year period 1935 through 1944 at the Royal Victoria Hospital, Montreal.

While this study provided me with valuable firsthand knowledge of the relative importance of various manifestations of hypertension as a cause of morbidity in the hospital population, it certainly convinced me that anyone who wanted to build up a series of cases in which the onset of hypertension had occurred under medical observation would probably have to start from scratch with his own case-finding methods, since there was apparently little or no spontaneous interest in this problem in the ordinary clinical records of hypertensive patients.

Another conclusion which gradually emerged during the study of these hundreds of hypertensive case histories was the extraordinary inconclusiveness of the commonly used criteria of "improvement" in the clinical course of hypertensive disease. This was reflected in the ease with which any enthusiastic protagonist of a particular method of treatment could justify his optimism in terms of apparent relief of symptoms,[3] or favorable changes in such "objective" indices as the height of the blood pressure, the size and shape of the heart shadow on the chest roentgenogram, the configuration of the T-waves of the electrocardiogram, the appearance of the vessels of the fundus oculi, and so on.

Now it is quite true that similar triumphs of enthusiasm over objectivity are extremely common in the assessment of therapeutic benefit in many diseases other than hypertension. However, the results of my first crude analysis of the problem led me to believe that, over and above the usual pitfalls due to wishful thinking and other human frailties, there were several purely statistical difficulties in the evaluation of therapeutic success in the management of hypertension, and that these difficulties were specifically related to shortcomings in the available data on the life history of the disease.

The long duration of the hypertensive state, the multiplicity of its clinical and pathologic manifestations, and the relative inadequacy of available methods of quantitative study of the functions of the affected organs, are only a few of the many obvious reasons for the incompleteness of our knowledge of the detailed life history of the disease. It is much harder, however, to find an acceptable explanation of the crucial difficulty which complicates all attempts to evaluate methods of treatment of hypertensive disease. It seemed to me that the chief stumbling block in this type of investigation is

the almost complete lack of authoritative data on the frequency of occurrence, in untreated patients, of the phenomena which are commonly used as criteria of objective benefit. As far as could be determined on the basis of my review of the Royal Victoria Hospital records, the lack of this vital information is due to the fact that it is only those investigators who wish to make a follow-up study of the effectiveness of some particular form of therapy who ever take the trouble to organize a system of periodic standardized reëxamination of patients in whom there exists no clinical indication for the tests in question, such as electrocardiograms, chest roentgenograms, or ophthalmoscopic examinations. Almost invariably, regardless of the merits of the treatment, instances are recorded of "favorable" changes after the institution of therapy, and it is natural enough for this apparently beneficial result to be ascribed to the effect of the treatment. Moreover, even if this classical *post hoc ergo propter hoc* fallacy is avoided, and a search is made for untreated controls, the only cases which are usually available for this purpose from the ordinary records of the hospital are those in whom the indication for repeated reëxaminations is some obvious deterioration of the patient's general clinical condition. Such patients are clearly not true controls, since their records will tend to underestimate the frequency with which so-called favorable changes would occur in the less seriously ill patients who are usually included in the average series of cases selected for the evaluation of a new therapeutic method.

Perhaps the foregoing analysis is not generally applicable to hospitals other than the one in which my studies were made, but I have tried to record as accurately as possible the point of view to which my year as Research Fellow of the American College of Physicians had brought me, since these ideas have provided the basic points of departure for my subsequent work. This project involves three main objectives, namely: (1) to undertake a case-finding program to select a group of patients in whom the transition from the normotensive to the hypertensive state occurred during a period of medical observation; (2) to record the results of a detailed clinical and laboratory study of each patient at more or less regular intervals from the onset of the hypertensive state to death in as many of these patients as possible, and (3) to try to improve the precision and accuracy of each of the tests used in the investigation to the point where the significance of any given change observed after the institution of some particular type of therapy can be evaluated in terms of the probability of occurrence of the same change in untreated patients, or in patients treated by some other method. In other words, we hope to combine a long-term study of the natural history of the disease with the provision of a standardized human bioassay service for the assessment of therapeutic methods.

During the long period of planning and organization which was required to initiate this program, I had the good fortune to be invited to participate in a large-scale follow-up study of sympathectomized patients at the Massachusetts General Hospital under the auspices of the Life Insurance Medical

Research Fund.[4] This appointment was of the utmost value in crystallizing my early concept of the correct approach to the problem, since it not only provided an opportunity to associate with a distinguished group of students of hypertension but also gave me free access to a great wealth of clinical material directly concerned with the study of the natural history of hypertensive disease. Here I refer to the splendid records which have been compiled in the Hypertension Clinic of the Massachusetts General Hospital during the past 20 years under the direction of Dr. Robert Stirling Palmer and his associates. I welcome this opportunity to express my great indebtedness to Dr. Palmer for all I have learned from him personally and from the study of his records. Indeed, it is fair to state that the project which we are now trying to carry out in Montreal is to a large extent a continuation of Dr. Palmer's general approach to this problem, with a few alterations in emphasis and certain refinements in technic and statistical method.

In general, my study of the records of 350 sympathectomized patients at the Massachusetts General Hospital confirmed my earlier concept of the basic causes of the difficulty of evaluating the effectiveness of therapy in hypertension, but a few additional points which were more apparent in Boston than in Montreal deserve special mention. I was particularly impressed with the virtual impossibility of employing the classical method of alternate untreated controls in any project in which some of the medical participants are sincerely convinced on intuitive grounds of the genuine effectiveness of the therapeutic method which is being investigated. This troublesome ethical difficulty may perhaps be overcome when it is reasonably certain that a definitive answer can be obtained by the study of a small series for a short period of time, as in the evaluation of the treatment of pneumonia by penicillin; but when it becomes obvious that a large number of patients must be denied access to a potentially life-saving procedure over a period of many years in order to satisfy the demands of statistical validity, it is necessary for the directors of the project to have an almost completely open mind on the issue.

The second point is a corollary of the first, namely, that if untreated controls are not available, it is essential that each patient be made to serve as his own control by insisting on a pre-treatment period of observation which is both long enough and detailed enough to provide a baseline sufficiently reliable to justify extrapolation into the post-treatment period with acceptable accuracy of prediction. This requirement is of special importance in dealing with irreversible therapeutic measures such as operations, since the method of alternate treatment and control periods cannot be employed. The inadequacy of baselines dependent on single pre-treatment observations was strikingly evident in the Massachusetts General Hospital data, not only for such notoriously labile factors as the blood pressure, but also for the electrocardiogram, the roentgenogram of the heart, the commonly used renal function tests, and such clinical observations as the ophthalmoscopic grading of the

ocular fundus. This point is of particular significance since it introduces an economic factor which greatly increases the difficulty of obtaining uniform statistical validity in any series which consists of a mixture of public and private patients.

Having thus outlined the basic objectives of our project, and indicated some of the pitfalls we hope to avoid, I shall try to describe the general organization which has been developed to carry out our long term study in Montreal. The provision of financial backing for such a slow-moving, unspectacular venture was a major hurdle to be surmounted, especially in view of the absence of direct emphasis on the development of new therapeutic methods, and the need for assured continuous financial support for a very long period. The problem was complicated still further by the necessity of using a part of the research funds to defray the per diem costs of hospitalization of some of the patients, since the average hypertensive patient in the early asymptomatic phase seldom has any spontaneous desire to enter a hospital and requires a few special inducements. For all these reasons, I would like to take this opportunity to express my sincere appreciation of the generosity of the corporation * which consented to underwrite the expenses of the first five years of the project.

Our clinical facilities consist of a self-contained Cardiovascular Unit which functions as a separate service within the Department of Medicine of the Royal Victoria Hospital. This unit, which is situated in the private patients' pavilion, is fully equipped for the performance of most of the usual clinical investigations involved in the study of hypertensive patients, and is air-conditioned throughout in order to provide the constant atmospheric conditions required for physiologic studies of the vasomotor system. The entire suite, complete with all routine intern, nursing, and housekeeping services, is leased from the hospital for an agreed annual rental which is paid by the research fund. This arrangement gives us the privilege of admitting patients without regard to their economic status, all patients being treated in every respect in a uniform manner. This system serves to protect the project from the serious limitation of clinical material which the rapidly increasing popularity of pre-payment plans for hospital insurance tends to impose on investigative programs whose scope is confined to public ward and outpatient clinic cases. The Cardiovascular Unit also provides space for follow-up examinations of ambulatory patients who do not require hospitalization.

The laboratory work of the project is handled by the Research Institute of Biophysics of McGill University, which adjoins the Royal Victoria Hospital. Since this Institute is under the same direction and is supported by the same donor as the Cardiovascular Unit, the all-important coördination between the clinical and laboratory services is easily maintained. The analytic requirements of the follow-up project occupy about half of the capacity of the Institute of Biophysics, leaving the remainder free for funda-

* The Bristol-Myers Company, New York, N. Y.

mental research in the general field of hypertension and arteriosclerosis. In keeping with the previously mentioned working hypothesis regarding the pathogenesis of the hypertensive state, the main research project of the laboratory is a systematic study of the chemical, physical and physiologic characteristics of pure samples of arteriolar smooth muscle prepared by microdissection of surviving blood vessels obtained by biopsy or during the performance of incidental surgical operations.

The medical staff of the unit consists of five full-time physicians and five part-time consultants, representing the specialties of ophthalmology, neurology, psychiatry, urology, and vascular surgery. The consultants are selected with great care on the basis of their interest in the general problem of hypertensive and arteriosclerotic disease, and every effort is made to obtain men of early middle age who, being firmly established in practice in Montreal, can be expected to maintain continuous interest in the project for its duration. We believe that adequate financial arrangements with all participants in a long-term research program are an important factor in ensuring sustained loyalty to the project under present economic conditions.

Our case-finding program must of necessity be a very slow process, because our early pilot studies revealed a very low incidence of patients with well documented histories describing the transition from the normotensive to the hypertensive state. However, our limited facilities and the time-consuming character of our investigative methods limit our capacity to about 50 new cases per annum, and our initial experience has shown that we can achieve this rate as long as we continue to receive the active coöperation of our colleagues in the Montreal area. An important factor in our favor at the present time is the rapidly expanding practice of periodic health examinations of presumably healthy individuals, not only in industry but also on the basis of personal initiative, inspired by campaigns for "positive health" organized by national bodies such as the Canadian Cancer Society.

The methods employed in the routine investigation of each case are entirely conventional, the only distinguishing feature being the emphasis on completeness and accuracy. For example, in taking the history, any item which depends entirely on the patient's unsupported statement is automatically assigned to a secondary level of credibility, the primary level being reserved for facts which can be independently verified by correspondence with physicians or hospitals in the case of medical data, or by reference to employers or other members of the family in the case of important personal data. Family histories of hypertension are established by reference to death certificates, or by personal examination of surviving relatives whenever possible. Similar precautions are employed in the physical examination. For example, in the ophthalmoscopic examination, separate gradings are made for each branch of the retinal vessels and each segment of the fundus in terms of 10 different factors, each abnormal finding being recorded in terms of degree, clock-face bearing, and distance from the nerve head. In addition, the precision of the entire grading is established by independent repeti-

tions of the whole examination. The same basic principle is applied to all the laboratory tests, each procedure being performed as frequently as is necessary to obtain a result which has a coefficient of variability of the same order of magnitude as the true physiologic fluctuation of the function which is being tested. Purely experimental procedures are not included in our battery of tests, because our project is intended merely to achieve an accurate clinical description of each patient's status in terms of the methods which are generally accepted as standard practice in the ordinary internist's evaluation of the hypertensive patient. We are extremely anxious to protect the project from the increasingly common and all too frequently justified criticism that patients who coöperate in an investigative project are sometimes subjected to procedures which involve a higher degree of inconvenience and risk than would be considered necessary for a similar patient on an ordinary clinical service.

As far as treatment is concerned, no effort is made to establish a series of "untreated controls," because we do not believe that such a project would be practicable, or ethically defensible, even if it were feasible. All our patients are treated, the majority by their own physicians, by whatever methods are considered best in terms of the patient's interests. No effort is made to interfere with the routine management or treatment of the patient, except insofar as the project serves as a composite consultant whose advice is perhaps more often taken than rejected. Our main function under this system is to act as an impartial monitor on the whole process by recording exactly what is done, and by trying to insist on the burdensome statistical safeguards which are essential to the evaluation of the real effect of the treatment on the course of the disease in the individual patient. By this compromise we feel that a mutually profitable synthesis can be achieved between the somewhat conflicting objectives of good medical practice and good statistical research. It is our hope that this approach will at least have the advantage of creating a system for evaluating the effectiveness of various methods of treatment in terms of an arbitrary but precisely defined and highly standardized set of criteria.

In conclusion, I would like to enter into the spirit of this tribute to the Research Fellowship program of the College by expressing the hope that our project will one day have the privilege of rendering an unqualified favorable judgment on some new therapeutic discovery made by one of the past, present or future Research Fellows of the American College of Physicians.

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CLINICALLY SIGNIFICANT DIFFERENCES BETWEEN PRECORDIAL ELECTROCARDIOGRAMS DERIVED FROM V AND CF LEADS *

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The best location for the distant electrode in obtaining precordial electrocardiograms is still a matter of dispute. Wilson, Johnston, Macleod and Barker [1] have recommended for this purpose an electrode whose potential they believe remains practically at zero and, therefore, unlike other distant electrodes, does not affect the potentials of the precordial electrocardiogram. Evidence in support of the validity of the Wilson electrode has been presented by Eckey and Froehlich,[2] Burger,[3] and Burger and Wuhrmann,[4] but Wolferth and Livezey [5] do not accept the conclusions of Wilson and his associates. Precordial electrocardiograms made with the Wilson electrode have been compared with those made with other distant electrodes in given cases by Kossmann and Rader [6] and Hecht,[7] who found no differences that would affect the clinical interpretation, and by Groedel,[8] Nagl,[9] Wallace and Grossman,[10] Alzamora Castro,[11] and Hull, Tucker and Weilbaecher,[12] among whose results there are instances of discrepancy.

The present study illustrates cases in which there are clinically significant differences between precordial electrocardiograms recorded in succession, once with the Wilson distant electrode (V leads [13]) and once with the distant electrode on the left leg (CF leads [13]), the precordial electrode remaining in place. By "clinically significant differences" is meant here the occurrence of abnormalities as judged by accepted criteria when one type of distant electrode is used, and the absence of these abnormalities when the other is used. In all cases, the abnormalities consist of T wave inversions and, in addition, in two cases there are abnormal Q waves. These abnormalities occur in the CF leads and are absent in the V leads. Such discrepancies show that at least in some cases the clinical interpretation may be influenced by the distant electrode. There was no evidence of heart disease in any of the cases, although there were questionable signs or symptoms in some. The general conclusion was that the CF leads gave false indications of abnormality, while the normal V leads were more consistent with the other clinical manifestations.

Any electrocardiogram represents the variations in the difference of

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potential between two electrodes regardless of where on the body the two electrodes are placed. The recorded potential of the precordial electrocardiogram at any moment is equivalent to the potential at the precordial electrode minus the potential at the distant electrode. The potentials of the latter are usually small compared to those at the precordium, and the slight differences among different distant electrodes do not usually affect the precordial electrocardiogram to a significant degree. Sometimes, however, the differences of potential of different distant electrodes are important. In the cases presented here, the potentials at the left leg were so much greater than those at the precordium or at the Wilson electrode that negative waves, Q and inverted T, occurred in CF leads where they are considered abnormal, whereas the corresponding deflections in the V leads were normally positive. Clinical evaluation led to the conclusion that such relatively high potentials at the left leg may occur in the absence of heart disease.

Methods

The electrocardiograms were recorded with the patient in the usual recumbent position. Standard limb leads, V and CF leads from the six standard positions [13] and augmented unipolar extremity leads [14] were obtained in each case. With the precordial electrode kept in place by an elastic belt, V and CF leads were obtained for each precordial position before moving to the next precordial position. In Cases 4, 5, 6 and 7, the original Wilson electrode [1] was used to obtain the V leads, and in Cases 1, 2 and 3, the Goldberger modification [14] of this electrode was used. The electrocardiograms were standardized so that 1 mv. equals approximately 10 mm.

These cases were selected from a larger number in which comparative studies were done. The latter were done when possible discrepancies were anticipated because of high or low potentials of QRS and T in the left leg lead (aV_F) as compared with the precordial leads. The cases described are those in which definite and significant differences occurred. Lesser differences were present in other cases. No attempt was made to estimate the frequency with which such discrepancies occur, but they apparently are not uncommon, since these cases were observed in a 300-bed hospital within a period of about one year.

The criteria for the normal V and CF leads on which the analysis of the following cases is based are taken from Barnes,[15] Kossmann and Johnston,[16] and Myers, Klein, Stofer and Hiratzka.[17] Barnes [15] found the T wave upright in $CF_{3,4,5}$ of 50 normal adult men and 50 normal adult women. T was frequently inverted or diphasic in CF_1, and it was diphasic in CF_6 of two of the men and in CF_2 of one of the women. Kossmann and Johnston [16] found T upright in $V_{2,3,4,5}$ of 30 normal adult men. T in V_1 was sometimes inverted. Myers and his associates [17] studied the V leads of individuals whose hearts were subsequently found to be normal by careful postmortem examination. They found T upright in $V_{4,6}$ of all 52 cases studied, and in

$V_{3,5}$ of all 25 cases studied, with two exceptions, namely, one isoelectric T in V_3 and one isoelectric T in V_6. T was inverted in V_1 in seven of 25 cases studied, and in V_2 in three of 52 cases studied. According to these criteria, then, an inverted T wave is abnormal in adults in either CF or V leads from precordial positions 3, 4 and 5.

Barnes [15] found no Q waves in CF_1 and CF_2. In $CF_{3,4,5,6}$ Q did not exceed 3.0 mm., and an R of at least 1.0 mm. was present. In other words, QS waves were not observed in any of the six precordial positions in any of 100 cases studied. Kossmann and Johnston [16] found no Q in $V_{1,2}$. Q in $V_{3,4,5}$ did not exceed 3.4 mm. There was at least a small R present in the five precordial positions studied (V_1 to V_5), and in $V_{3,4,5}$ R was at least 6.0 mm. Myers and his associates [17] found QS waves in $V_{1,2}$ in some of the cases. Q in $V_{3,4,5,6}$ did not exceed 2.0 mm., and R in these leads was at least 2 mm. According to these criteria, then, QS waves are not found in normal electrocardiograms in either the CF or V leads from precordial positions 3, 4, 5 and 6, and the Q waves in these positions when present are small.

Case Reports

Case 1. A 64 year old white man had chronic pulmonary emphysema and had suffered from severe bronchial asthma for 10 years. The vital capacity was greatly reduced (0.8 liter). The physical examination, the roentgenogram of the heart, the venous pressure, and the arm-to-tongue (calcium gluconate) and arm-to-lung (ether) circulation times revealed no evidence of cardiovascular disease. The blood

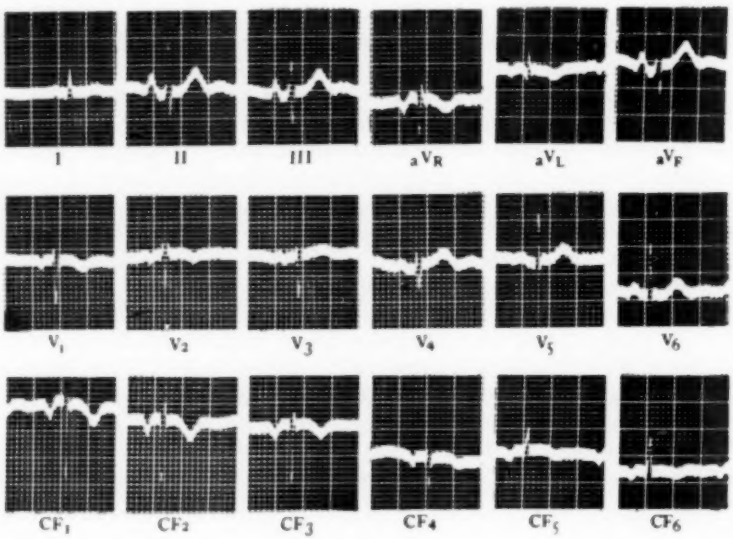

Fig. 1.

pressure was normal. Roentgenograms of the chest showed hyperaeration of both lungs and an elongated heart in the vertical position.

There are inverted T waves in all the CF leads (figure 1). The T waves are inverted in $V_{1,2}$ but they are upright in $V_{3,4,5,6}$. In $CF_{1,2,3}$ there are no early R waves, the initial parts of QRS in these leads being Q waves. In the corresponding V leads, however, there are normal, early R waves. The P waves in the CF leads are deeply inverted, whereas those in the V leads from the left side of the precordium are upright. The P waves in standard Leads II and III and in Lead aV_F are large. The P, R and T are relatively high in aV_F.

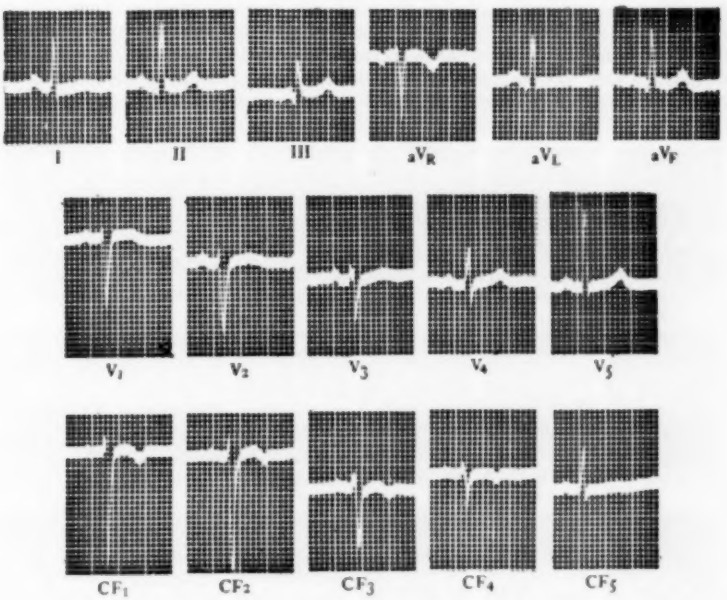

FIG. 2.

The prominent P waves in Leads II, III and aV_F are such as have been observed with cor pulmonale and have been attributed to right atrial hypertrophy or strain.[18, 19, 20, 21, 22] However, such P waves have been observed also in the absence of cor pulmonale or right atrial hypertrophy or strain,[20, 23, 24, 25, 26] and have been attributed by different authors to change in position of the heart as a result of the inspiratory position of the chest in emphysema, to mediastinal shift, and to lability of the vegetative nervous system. The electrocardiograms are not characteristic of right ventricular hypertrophy.[27, 28, 29]

From the CF leads, myocardial infarction might have been suspected because of the deep Q in $CF_{1,2,3}$ and the minute R in CF_4 in association with inverted T waves. There was nothing in the history to suggest the occurrence of an infarct or of angina pectoris. The clinical impression was that there was no heart disease. It was believed that the changes in the CF leads were related to the altered position of the heart resulting from the inspiratory position of the chest.

Case 2. A 39 year old white woman was admitted to the hospital for study because an inverted T wave in Lead IV F was found in a routine check-up. Her only symptoms, elicited in response to leading questions, were pain in the region of the thoracic spine and slight shortness of breath on moderate exertion.

The physical examination, the roentgenogram of the heart, the venous pressure, the arm-to-tongue (calcium gluconate) and arm-to-lung (ether) circulation times and a two-step exercise test[30] revealed no evidence of heart disease. The blood pressure was normal.

In the first comparative study (figure 2) there are inverted T waves in $CF_{1,2,3,4}$, whereas in the corresponding V leads the T waves are upright. The standard limb leads and augmented unipolar extremity leads are normal, although T_1 is somewhat low. T in aV_F is relatively high. In a subsequent comparative study about one year later, T is inverted in V_2 as well as in $CF_{2,3,4,5,6}$, T_1 is low and diphasic and T in $V_{4,5}$ is low. At this time T_1 and T in V_2 were considered abnormal as well as the CF leads, but it was the opinion of several examiners that there was no clinical heart disease.

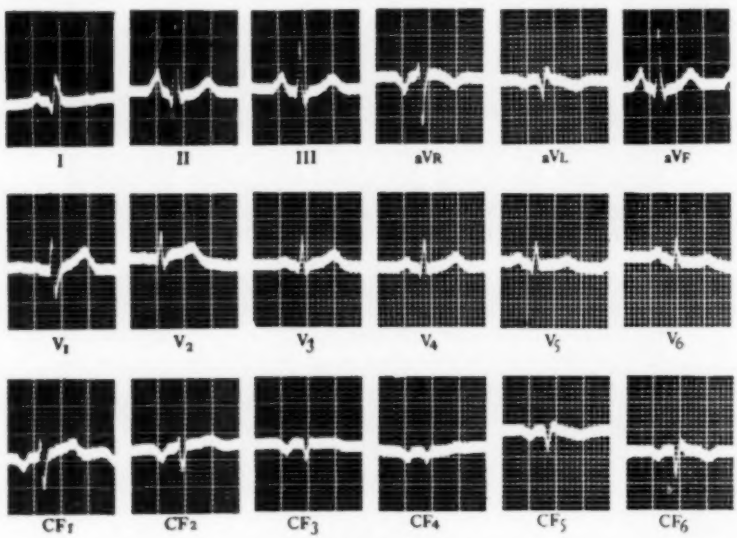

FIG. 3.

Case 3. A 33 year old white man had bronchogenic carcinoma, and the right lung was removed. Roentgenograms showed the heart displaced far to the right and into the posterior part of the chest. The history and physical examination revealed no evidence of cardiovascular disease. The blood pressure was normal.

The electrocardiograms (figure 3) are understandardized about 10 per cent. There is a large peaked P wave in Lead II and a prominent P wave in Lead III. There are Q waves in the three standard limb leads. Q_1 is rather wide, although its amplitude, like that of $Q_{2,3}$, is not outside the accepted limits of normal. In the precordial V leads the transition zone is shifted towards the right. There are relatively large Q waves in $CF_{3,4,5,6}$ and inverted T waves in $CF_{5,6}$. R and T in aV_F are high.

As in Case 1, the pulmonary disease and the prominent P waves in Leads II and III suggested possible cor pulmonale, but there was no other evidence to support this diagnosis. From the CF leads a diagnosis of anterior wall infarction might have been made because of the relatively large Q waves in Leads $CF_{3,4,5,6}$ and the inverted T waves in $CF_{5,6}$. There was nothing in the history to suggest the occurrence of an infarct or of angina pectoris. It was believed that this patient did not have heart disease and that the extreme displacement of the heart accounted for the electrocardiographic changes.

The patient died at another hospital and no autopsy was performed.

Case 4. An obese 60 year old white man suffered from brief episodes of fainting and mental depression which were attributed to cerebral arteriosclerosis. He complained of shortness of breath on moderate exertion. The physical examination, the roentgenogram of the heart, the venous pressure, and the arm-to-tongue (calcium gluconate) circulation time revealed no evidence of heart disease. An exercise test [20] yielded questionable results; there were no S–T depressions, but T_1, low in the control, became slightly inverted following exercise.

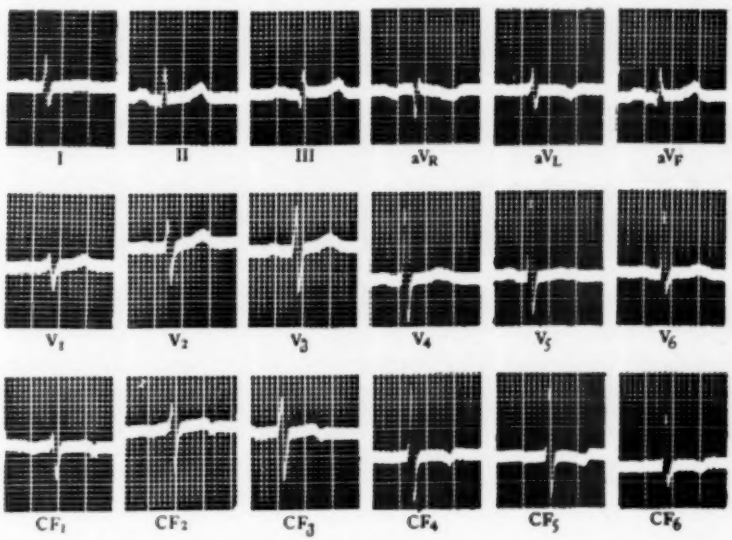

FIG. 4.

There are diphasic T waves in $CF_{1,2,3}$ and inverted T waves in $CF_{4,5,6}$ (figure 4). The T waves in the corresponding V leads are upright, and there is slight notching of T in $V_{4,5}$. In the standard limb leads T_1 is low. There is a deep Q_3. The Q in aV_F is small, however, so that the Q_3 is probably not indicative of abnormality. T is relatively high in aV_F. The possibility of coronary arteriosclerotic heart was considered, but the evidence was minimal.

Case 5. A 65 year old white woman had hypertrophic arthritis of the spine and knees. She gave a history of slight shortness of breath on climbing two flights of stairs and of occasional slight swelling of the ankles late in the afternoon. The blood pressures were: right arm 170/80, left arm 163/84 mm. Hg. The physical examina-

tion, the roentgenogram of the heart, the venous pressure, and the arm-to-tongue (calcium gluconate) circulation time revealed no evidence of heart disease. Edema was not observed in spite of the history.

The control electrocardiogram at rest for the two-step exercise test [30] showed an inverted T in IV F as had previously been observed. Following exercise there were no S–T deviations, but T in IV F became upright. According to the criteria of Master, Friedman and Dack,[30] this is an abnormal response indicating coronary insufficiency. However, reversal of T in precordial leads from inverted to upright following exercise has been observed in the absence of heart disease.[31]

There are diphasic or inverted T waves in the CF leads (figure 5). T is diphasic in $V_{1,2}$ but upright in $V_{3,4,5,6}$. The standard limb leads and unipolar extremity leads are normal. T in aV_F is relatively high. In electrocardiograms recorded at other times, T in V_4 is low and notched but upright.

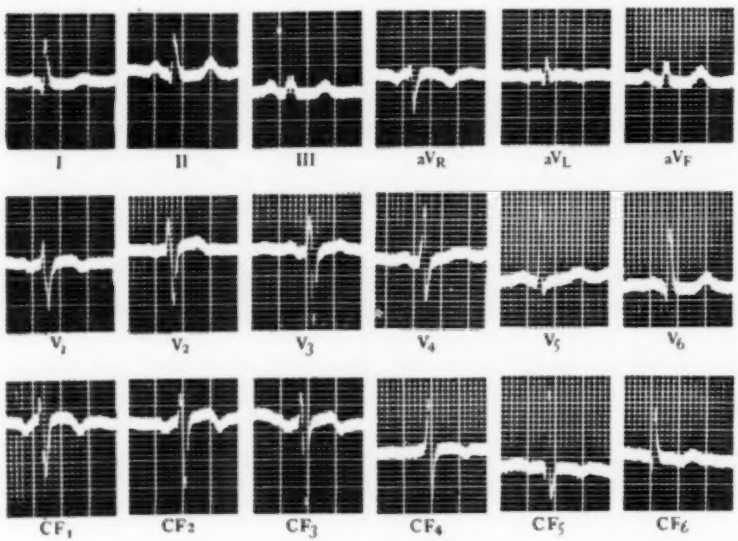

FIG. 5.

The diastolic pressure was not elevated at any time. The blood pressure was interpreted as consistent with arteriosclerosis of the aorta; there was no evidence of other conditions which may produce elevation of systolic blood pressure without elevation of diastolic blood pressure, namely, aortic insufficiency, thyrotoxicosis, or heart block. The possibility of coronary arteriosclerotic heart disease was considered, but the evidence was minimal.

Case 6. A 53 year old white man had paroxysms of shortness of breath and at times more persistent dyspnea, believed to be due to bronchial asthma. He had had chronic cough for many years. The paroxysms of dyspnea were associated with a sensation of faintness and with substernal discomfort. The latter was unrelated to exertion or emotional stress and did not radiate. Expiratory wheezes and coarse râles were heard over the chest. The blood pressure was normal. A systolic murmur of moderate pitch and intensity was heard over the precordium and was maximal

at the apex. The roentgenograms of the heart, the venous pressure, and the arm-to-tongue (calcium gluconate) and arm-to-lung (ether) circulation times revealed no evidence of heart disease.

The patient received adequate amounts of digitalis with no effect on the respiratory difficulty. Following the two-step exercise test,[30] T_2 and T_3, upright in the control electrocardiogram at rest, became diphasic; there were no depressions of the S–T junction greater than 0.5 mm.

The T waves are diphasic in CF_4 and inverted in $CF_{5,6}$ (figure 6). The T waves in the corresponding V leads are upright. T in aV_F is relatively high. The standard limb leads and unipolar extremity leads are normal, although T_1 is somewhat low. In electrocardiograms obtained at other times, T in $V_{5,5}$ is low and notched but not inverted. It was believed that there was no heart disease.

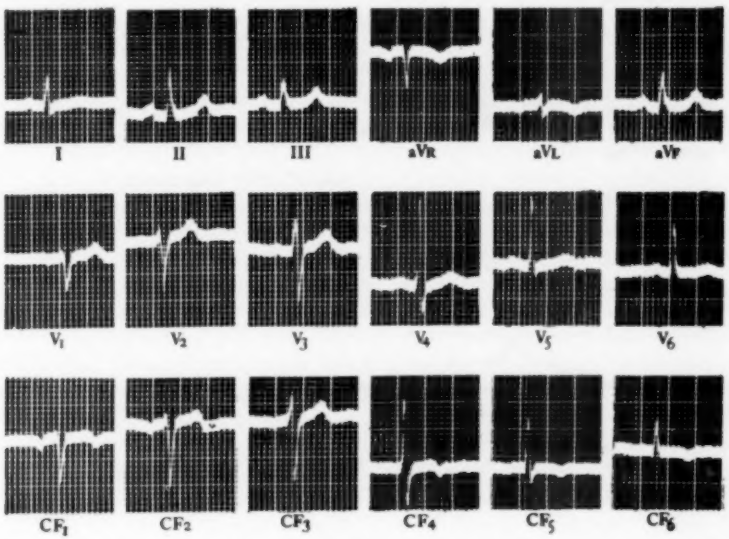

FIG. 6.

Case 7. A 48 year old white man was admitted to the hospital in May, 1947, because of recurrent lower abdominal pain of eight years' duration. There were numerous white blood cells in the urine, *B. coli* was cultured from urine obtained from the right renal pelvis, and pyelograms showed poor function and hypoplasia of the right kidney and pronounced hypertrophy of the left kidney. The abdominal pain was attributed to chronic right pyelonephritis.

In 1936 the patient had had intermittent claudication, bluish discoloration of the toes, superficial ulcers of the feet and legs, superficial phlebitis of the legs, and questionable atrophic changes in one finger. A diagnosis of thromboangiitis obliterans was made, and there was considerable improvement following lumbar sympathectomy in 1939. By 1947 the patient still noted no discoloration of the toes except occasionally in cold weather, and cramps in the legs occurred only after long walks.

Since 1946 the episodes of abdominal pain were followed after an interval of several hours by pain in the xiphoid and precordial regions. The chest pain was steady rather than paroxysmal, unrelieved by rest and did not radiate.

The physical examination revealed no evidence of heart disease. The blood pressure was normal. Roentgenograms showed the heart to be of the transversely oval type with a rounded left ventricular border and with a transverse diameter at the upper limit of normal. A two-step exercise test [20] showed no abnormalities.

The T waves are inverted in $CF_{4,5}$, whereas they are upright in the corresponding V leads (figure 7). T in aV_F is relatively high. Some of the complexes in Leads III and aV_F show a Q wave, while others show a small R as the initial QRS deflection.

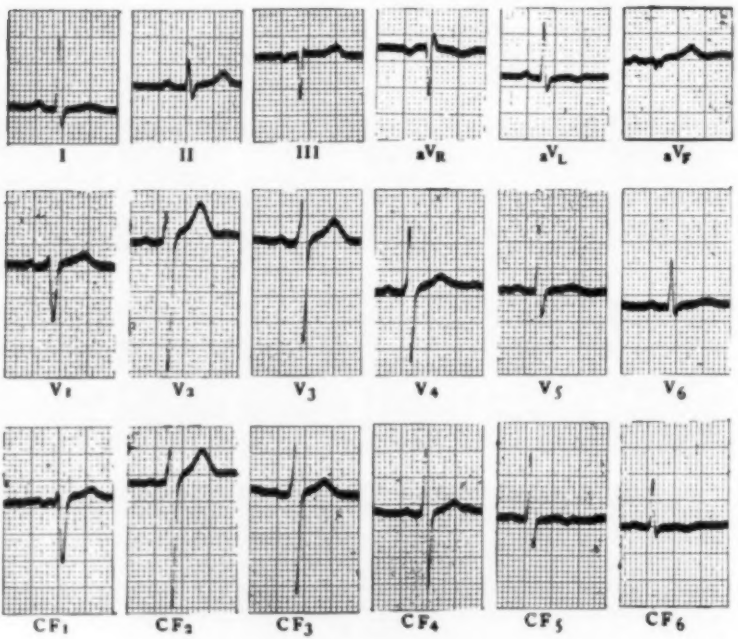

FIG. 7.

The chest pain was not characteristic of angina pectoris, and this was consistent with the negative exercise test. While the possibilities of coronary arteriosclerotic heart disease and the rarely-occurring involvement of the coronary arteries by thromboangiitis obliterans were considered, the final impression was that there was no heart disease.

DISCUSSION

Kossmann and Rader [6] studied eight patients with heart disease and one individual without heart disease and found no clinically significant differences in precordial electrocardiograms recorded in turn with a distant electrode of the Wilson type, one placed on the left leg, and one placed just medial and below the angle of the left scapula. In normal individuals Hecht [7] rarely found the distant electrode to have a conspicuous influence

on the precordial T wave. However, he considered it conceivable that an unusually high potential at the left leg during the recording of the T wave might cause a diphasic or even an inverted T wave in $CF_{5,6}$.

In one case Groedel [8] observed a "completely inverted R" in a CF lead, whereas the R was normally upright in the corresponding V leads and other leads. In some cases Q waves were present in the V leads and absent in the corresponding CF leads, while in other cases there were Q waves in CF leads which were absent in corresponding V leads. In all these cases the Q was present in the CR leads. Since the sizes of the Q waves are not given, and the electrocardiograms are not illustrated, it is not possible to determine the bearing of these differences on the clinical interpretation. Groedel [8] noted differences between CL leads on the one hand and V leads and other leads on the other hand in two cases, but since the CL leads are not often used, and adequate normal criteria for these leads are not available, these differences will not be discussed.

Nagl [9] illustrates an electrocardiogram of a patient who was believed to have angina pectoris in which the T waves are inverted in $CF_{2,4,5}$, whereas they are upright in the corresponding V leads. In a case reported by Alzamora Castro [11] the T waves are inverted in $CF_{2,4,5,6}$, whereas they are upright in the corresponding V leads. Hull, Tucker and Weilbaecher [12] describe normal V leads and abnormal CF leads in four cases in which there was no evidence of heart disease.

Wallace and Grossman,[10] after comparing $V_{2,4,5}$ with the corresponding CF leads of 91 individuals with normal and abnormal electrocardiograms, conclude that the differences are minor and that the V leads offer little if any diagnostic information not obtainable with the homologous CF leads. Nevertheless, in three of their cases of posterior wall infarction T is inverted in V_5 and upright in CF_5. Adherents of the Wilson electrode would maintain that the inverted T in V_5 indicates anterior or lateral wall involvement, information not available in the CF leads, and that the upright T in CF_5 is a false picture due to the low potential at the left leg electrode during the recording of the T wave, the latter being demonstrable as an inverted T wave in the left leg lead, V_F or aV_F. In a case reported by Alzamora Castro,[11] this discrepancy is involved in determining whether or not a second infarction had occurred. This author observed a patient who had an infarct of the posterior wall. Twenty days following the original infarction there was another acute episode of pain, and the V leads now showed T wave changes indicative of extension of the infarct laterally and anteriorly, whereas the CF leads showed no significant change.

Other studies comparing precordial electrocardiograms obtained with distant electrodes at different sites, though not including leads obtained with the Wilson electrode, were carried out by Geiger,[32] Wolferth and Wood,[33] Liebow and Cushing,[34] Lipton,[35] and Mortensen and Warburg.[36]

The discrepancies between the V and CF leads in the cases presented here were due to high potentials at the left leg compared to the potentials at

the precordium and at the Wilson electrode. The unusual positions of the heart in Cases 1 and 3—in the one case the extremely vertical position associated with emphysema, and in the other case the displacement to the right and posteriorly following pneumonectomy—suggested that such potentials may result from changes in the position of the heart and its relationships to adjacent structures. In these cases also there were possible explanations for low precordial potentials, namely, the hyperaerated lung interposed between heart and precordium in the case of emphysema, and the increased amount of lung interposed between heart and precordium in the case of pneumonectomy due to posterior displacement of the heart, air and lung being poor electrical conductors. In the other cases there were no such apparent explanations, but it is possible that changes in cardiac position and relationships less extreme than those obvious in roentgenograms may still produce sufficiently high potentials at the left leg in the absence of heart disease to account for CF leads which are considered abnormal by generally accepted criteria. Other factors may be involved which are not apparent in clinical studies.

No cases were observed in this study with significant discrepancies associated with low potentials at the left leg. Such discrepancies were described by Wallace and Grossman [10] and Alzamora Castro [11] and have already been discussed.

Some possible limitations of clinical evaluation for determining which leads are preferable should be mentioned. Cardiac abnormalities may be overlooked by the usual means of investigation. Also, it is at least conceivable that electrocardiographic changes may antedate other evidence of heart disease. Nevertheless, it was not believed that these hypothetical limitations negated the evidence of all seven cases, and the general conclusion was that these were cases in which the CF leads gave false indications of cardiac disease. There was no definite evidence of heart disease in any of the cases, and at most there were doubtful symptoms or signs in some. In Cases 1 and 3, in which the diagnosis of myocardial infarction might have been made from the CF leads, the clinical superiority of the V leads was particularly evident.

Summary and Conclusions

Cases are reported in which there were clinically significant differences between precordial electrocardiograms derived from V and CF leads recorded in succession, the precordial electrode remaining in the same place. Abnormalities occurred in the CF leads, in all cases inverted T waves and in two cases abnormal Q waves, whereas the corresponding V leads were normal. There was no definite evidence of heart disease in any of the cases, although there were questionable symptoms or signs in some. The general conclusion is that the CF leads gave false indications of cardiac disease, while the normal V leads were more consistent with the cardiac status. In two of the cases the diagnosis of myocardial infarction might have been made

from the CF leads, when there was nothing in the history to suggest the occurrence of infarct or angina pectoris. The discrepancies were due to high potentials at the left leg compared to the potentials at the precordium and at the Wilson electrode; such potentials may occur in the absence of heart disease and may be related to alterations in the position of the heart and its relationships to adjacent structures.

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THE RELIEF OF PEPTIC ULCER PAIN BY TETRAETHYL AMMONIUM CHLORIDE *

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THE promising application of vagotomy to the therapy of peptic ulcer has stimulated study of pharmacologic agents capable of depressing vagal activity. One such drug is the quaternary ammonium compound, tetraethyl ammonium chloride. In 1945 and 1946 Acheson and Moe,[1, 2] working with animals, demonstrated that the tetraethyl ammonium ion blocks transmission of nerve impulses through autonomic ganglia. Later, Lyons et al.[3] studied the effects of this blockade in man. One of these effects was the cessation of propulsive gastrointestinal motility as observed fluoroscopically with the barium meal. They noted that pain resulting from peptic ulcer was relieved following administration of tetraethyl ammonium. This observation caused us to administer the drug to several patients on our wards whose pain due to peptic ulcer had been difficult to manage. Immediate disappearance of pain in these patients was dramatic, and they could be maintained pain free by repeating this medication at intervals of 12 hours. As a result of this experience we entered upon a more complete observation of the use of tetraethyl ammonium for relief of the pain of peptic ulcer.

Since the initiation of this study further reports have been published confirming the observation of Lyons that tetraethyl ammonium stopped gastrointestinal motility, particularly of the stomach. Holt, Lyons, et al.[4] and Dodds, Ould, and Dailey[5] utilized the technic of roentgen-ray observation after the barium meal. Both groups comment upon the similarity of the inactive stomach following the administration of tetraethyl ammonium to that seen after vagotomy. Brown, Posey and Gambill,[6] utilizing a gastric balloon and manometer, found the same abrupt quieting of the stomach after administration of tetraethyl ammonium and noted that two patients with ulcer pain were relieved of pain upon the administration of this drug during motility studies.

MATERIAL

From July 1, 1947 to July 1, 1948, 70 male patients were admitted to the medical service in whose cases the diagnosis of peptic ulcer was established by clinical and roentgenologic study. Of these, 30 proved to be readily

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amenable to simple therapeutic procedures of rest, diet, antacids and mild sedation. Forty were considered to be less amenable to simple therapy by reason of severity of symptoms, recurrence and chronicity, or refractoriness of the ulcer and/or the patient to standard treatment. The high proportion of more severe cases is explained by the character of hospital versus office practice. Of the latter group of 40, 27 cases presented pain as an outstanding symptom. These 27 cases form the basis of this report. Among these, one ulcer was gastric in location, three were at the pyloric ring, 22 were duodenal and one was at a gastro-jejunal stoma. Four of the duodenal ulcers and one pyloric were penetrating, two were complicated by subtotal pyloric obstruction, and one by hemorrhage.

Method

In the five cases of penetrating ulcer, or with penetrating type pain, administration of tetraethyl ammonium chloride *† was begun immediately upon admission because the need to control pain and clarify diagnosis was paramount. TAC administration was initiated upon admission by physicians other than the authors in four other cases. Two of these received but one dose of the drug.

Eighteen cases were first maintained on standard management as a control. At this hospital, this treatment consists of bed rest, tincture of belladonna minims 10 three times daily, phenobarbital .5 grain four times daily, six ounces of half milk-half cream, and one-half ounce of aluminum hydroxide—magnesium trisilicate gel (Gelusil) on alternating hours from 7:00 a.m. to 10:00 p.m. If pain was not lessened, the antacid was changed to Sippy powders. Where some improvement was manifest the diet was liberalized by addition of very bland foods, such as junket, soft cooked eggs and purees. A predigested protein supplement was given with milk in all cases. Where nocturnal pain was prominent the stomach was emptied by tube at 10:00 p.m. and one ounce of gel was introduced before the tube was withdrawn.

The 30 cases receiving relief from this treatment have been excluded from this report as amenable to simple therapy. The administration of TAC was begun upon the 18 control cases at varying intervals after beginning the above treatment. The decision to administer TAC came when standard treatment seemed to offer the patient no relief of pain, or when incomplete reduction of pain had reached a stationary level. When administration of TAC was begun the diet was liberalized and belladonna, phenobarbital and antacids were discontinued.

In our first case TAC was administered intravenously; thereafter it was given exclusively by the intramuscular route. Dosage was standardized at 500 mg. Eighteen cases were administered this dosage two times daily, six

* Hereafter referred to as TAC for sake of brevity.

† We wish to acknowledge the gift of a generous supply of tetraethyl ammonium chloride (Etamon) from Parke, Davis & Company for purpose of this study.

cases one time daily. Three cases received a single dose. Duration of administration varied widely.

In the majority of those cases where chronicity, location of ulcer, or behavior on standard treatment indicated surgery, no attempt was made to delay this surgery to afford continued observation of the relief of pain by TAC.

Results

Complete relief of pain of peptic ulcer within five to 10 minutes after intramuscular administration of TAC was the rule. Recurrent pain could be consistently relieved by repetition of the drug. The five cases of penetrating ulcer admitted with pain simulating perforation were outstanding examples. Penetration or deep scarring was shown in three of these cases later subjected to surgery. A case history of one is given for better illustration of the response seen in this group.

Case 1. A 30 year old restaurateur first developed symptoms of epigastric distress three years ago. After hospitalization and examination he was given a medical discharge from the armed forces with a diagnosis of peptic ulcer. In the two years following his discharge he continued to be bothered several times a month with episodes of burning, cramping epigastric pain, coming on two or three hours after meals and frequently at night. For two months prior to entering hospital the patient had limited his food intake to goat's milk and raw eggs, with frequent use throughout the day of alkaline powders. In spite of this, symptoms became worse so that one week before admission pain became constantly present and was associated with nausea and vomiting. Examination upon admission showed a well-developed and well-nourished adult male in acute distress. There was marked abdominal tenderness and rigidity, especially in the epigastrium. The patient was afebrile. A roentgenogram of the abdomen in the upright position showed no free air in the abdominal cavity. Epigastric pain occurred in frequent paroxysms which would cause the patient to double up in an effort to seek relief. During these paroxysms the blood pressure would rise from a normal level to 190/100 mm. Hg.

The patient was given 500 mg. of TAC intravenously and within 30 seconds after beginning the injection he became completely free of symptoms. After the completion of the intravenous injection he was given 500 mg. of TAC intramuscularly. Symptoms recurred in 12 hours, and thereafter tended to recur daily in the early morning hours. His comfort was then maintained on a single daily injection of 500 mg. of TAC given at 5:00 a.m. This was maintained until subtotal gastric resection on the sixteenth hospital day. The pathologic specimen showed a penetrating ulcer of the duodenum immediately distal to the pylorus. The ulcer was sharply punched out and had a floor of necrotizing granulation tissue with fibrosis extending through the muscularis and serosa. There was considerable induration and formation of adhesions about the anterior wall of the duodenum, extending posteriorly to the pylorus.

In the four cases where administration of TAC was not initiated by the authors, relief of pain was also consistent. In two cases this therapy was not pursued because of objection of the patient to hypodermic medication or discomfort at the site of administration.

The 18 cases submitted to a control period of observation under standard therapy before the administration of TAC responded upon its exhibition

with equally rapid relief of pain. Frequency of administration of TAC in all cases was determined by individual tendency to return of pain. Eighteen cases were given the drug twice daily at 12 hour intervals; six cases received this medication daily or less often; three cases received a single dose.

Table 1 lists patients' ages, symptoms and their duration, roentgen-ray findings, duration of, and response to, control period of standard therapy, response to administration of TAC with dosage and frequency, disposition of case, and pathologic findings where surgery was performed.

Two additional brief case reviews are offered in example of pain relief by TAC in comparison with progress on standard therapy.

Case 18. A 53 year old oil-field worker had a three-year history of almost constant epigastric pain with associated nausea. For three weeks before entering the hospital he had limited his diet to milk, raw eggs and Cream of Wheat. He had used alkaline powders frequently. This regime resulted in but minimal relief. Roentgen-ray examination upon admission showed a markedly deformed duodenal bulb. He was treated for 14 days with a careful, standard regime. This period resulted in no relief beyond that which he had attained before hospitalization. Initial administration of 500 mg. of TAC relieved both pain and nausea. He was maintained in comfort with administration of TAC once a day until subtotal gastrectomy 14 days later. A duodenal ulcer with marked scarring and deformity of the duodenum was found.

Case 23. A 49 year old laborer had a 16 year history of repeated attacks of epigastric pain, with nausea and vomiting. Frequency and severity of attacks had gradually increased. Roentgen-ray examination upon admission showed a deformed duodenal bulb, with 60 per cent gastric retention of barium at five hours. He was treated with standard therapy for three days with no improvement in symptoms. Twice daily administration of TAC was begun in 500 mg. doses. Pain was relieved immediately. Nausea and vomiting disappeared as nightly aspirations fell from a level of 1,000 c.c. to 200 c.c. over a period of 12 days. Roentgen-ray examination at this time showed no five hour retention. Administration of TAC was then discontinued. He remained free of pain and nausea, but gastric aspirations at 10 p.m. rose to a quantity of 1,000 c.c. after 11 days. Twice daily administration of TAC was resumed. Within four days evening gastric aspiration fell to 300 c.c. A subtotal gastrectomy and abdominal vagotomy were done. A sharply punched out duodenal ulcer with a floor of necrotic granulation tissue was found. There was marked contracture and deformity of the bulb with adhesion to the pancreas.

In summary, all cases of proved peptic ulcer with severe pain responded to intramuscular administration of TAC in 500 mg. doses with immediate relief of pain. This response could be elicited as often as necessary to maintain each case pain free for the duration of the use of this drug.

Discussion

Consideration of the mechanism of this relief of the pain of peptic ulcer is in order. To this purpose a brief review of the physiology of gastroduodenal innervation is drawn largely from standard texts on physiology.[7, 8]

The stomach and duodenum receive their nerve supply from the vagus and from splanchnic sympathetics of the level thoracic five through thoracic eleven. Afferent fibers are present in both vagus and sympathetic trunks.

TABLE I

Case	Age	Symptoms†	X-Ray Findings	Standard Therapy Days	Result	T.A.C.	Result	Disposition Pathologic Findings
1*	30	Almost constant pain, nausea, vomiting for 3 years. Admitted with pain suggesting perforation. Pain xxxx.	Ulcer crater in pyloric canal.	0	—	500 mg. (I.V.) then 500 mg. daily for 14 days.	Immediate control of all symptoms.	Subtotal gastrectomy. Penetrating ulcer of duodenum at pylorus.
2	28	Slowly increasing recurrence of epigastric discomfort over 11 years. Hemorrhage one year ago. Continuous symptoms since. Nausea, vomiting, penetrating type pain xxxx.	Clover leaf bulb.	0	—	500 mg. 2 ×day for 4 days. P.R.N. for pain less often than daily.	Complete control of symptoms. No pain.	Subtotal gastrectomy and abdominal vagotomy. Duodenal ulcer with deep scarring.
3	25	4 years of frequently recurrent pain, nausea and vomiting. Hemorrhage 4 years ago. Admitted vomiting. Penetrating type pain xxxx.	Irregular and tender bulb.	0	—	500 mg. on admission. P.R.N. averaging q other day for 14 days.	Immediate relief. Controlled in comfort upon any recurrence of pain.	Subtotal gastrectomy and abdominal vagotomy. Duodenal ulcer with moderate scarring.
4	59	10 years of recurrent epigastric distress. Perforation two years ago. Admitted with penetrating type pain xxxx.	Irregular and tender bulb.	0	—	500 mg. 2 ×d. for 3 days.	Complete control of all symptoms. No pain.	Return to work this hospital after one week. Duration of remission 8 months.
5	59	Six months of recurrent epigastric pain, nausea and vomiting. Admitted with penetrating type pain xxxx.	Spastic, irregular and tender bulb.	0	—	500 mg. at admission and 2 ×d. for 12 days.	Immediate control of symptoms. No pain.	Discharged arrested.
6	38	Onset hemorrhage, recurrent pain and nausea several times yearly for 5 years. Pain xxx.	Large crater pyloric canal.	18	Reduction of pain to xx, remainder of symptoms little changed.	500 mg. 2 ×d. for two days, then daily for 3. On return 2 ×d.	Immediate freedom from all symptoms. Discharged at pts. request in 10 days. Return in 2 months with severe exacerbation, and similar relief obtained.	Subtotal gastrectomy. Large ulcer pyloric canal.
7	20	Recurrent pain, nausea and vomiting 1½ years. Marked anxiety. Pain xxx.	Ill defined bulb with ulcer defect.	26	Irregular response. Pain reduced to x. Nausea and vomiting persisted.	Single dose of 500 mg. before surgery.	Complete relief of symptoms for 24 hours.	Subtotal gastrectomy. Small duodenal ulcer.

* More detailed case report in text.

† X used to denote degree of pain on familiar 1 to 4 estimation. XXXX used only where pain of sufficient degree to warrant relief by narcotic or other measure.

TABLE I—*Continued*

Case	Age	Symptoms	X-Ray Findings	Standard Therapy Days	Result	T.A.C.	Result	Disposition Pathologic Findings
8	51	Severe pain, nausea and vomiting about once yearly for 20 years. Pain xxx.	Ill defined duodenal bulb.	2	No improvement, pain xxx.	500 mg. 2 ×day for two days.	Immediate relief of all symptoms. Then response to standard therapy.	Discharged as arrested.
9	25	Repeated hospitalization over 3 years for severe pain, nausea, vomiting. Pain xxx.	Irregular bulb clover leaf.	14	Partial control of symptoms. Pain xx.	500 mg. 2 ×day for 22 days.	Complete relief of all symptoms.	Transthoracic vagotomy.
10	50	Chronic epigastric distress for 20 years. Perforation repair and gastroenterostomy 15 years ago. Pain xxx.	Partial block of stoma with partial jejunal obstruction.	2	Relief of frequency of spasms of pain. Intensity unchanged.	500 mg. daily for 20 days.	Relief of pain. Some epigastric fullness persisted.	Subtotal gastrectomy. Resection of jejunum with side to side anastomosis. Stomal ulcer and scarring.
11	26	Recurrent pain, nausea, vomiting for 3 years. Severe neurotic. Pain xx.	Negative except bulb tenderness.	12	Pain reduced to x. Relief of nausea and vomiting. Discharged at own request. Return in 9 days, original symptoms.	500 mg. 2 ×day 12 days.	Complete and immediate relief in comparison with first admission.	Again discharged at own request. Neurosis prevented cooperation with therapy.
12	34	8 years of frequent pain, nausea, vomiting. Pain xx.	Clover leaf bulb.	5	No relief of symptoms.	500 mg. daily for 10 days.	Complete control of symptoms. No pain.	Abdominal vagotomy. Small duodenal ulcer present.
13	34	3 years of recurrent episodes with pain most prominent. Pain xxx.	Clover leaf bulb. 5% retention at 5 hours.	60	Periods of several days of relief with recurrent distress and pain. Usual persistent pain x.	500 mg. 2 ×d. days.	Complete control of symptoms. No pain.	Transthoracic vagotomy.
14	32	4 years of recurrent pain, slight nausea. Repeated hospitalization. Pain xx.	Irregularity and tenderness of bulb.	30	Irregular response with recurrent episodes of pain.	500 mg. 2 ×d. for 60 days.	Complete control of symptoms. No pain.	Transthoracic vagotomy.
15	30	12 years of frequent episodes of nausea, vomiting and pain xxx.	Irregular and tender bulb.	4	No relief.	500 mg. daily 12 days	Complete relief of pain and vomiting. Slight nausea persisted.	Abdominal vagotomy. Small duodenal ulcer, scarring and induration.
16	41	4 years of recurrent epigastric pain. Pain xxx.	Hyperperistalsis irregular bulb.	35	Improvement in general comfort, pain persisted at x.	500 mg. 2 ×d. for 30 days.	Complete control of symptoms. No pain.	Subtotal gastrectomy. Duodenal ulcer, healed to microscopic size.
17	54	2 years of recurrent pain, nausea, vomiting. Large neurotic element. Pain xxx.	Ulcer crater lesser curvature pars media of stomach. Confirmed by gastroscopy.	5	No improvement.	500 mg. 2 ×d. 18 days.	Complete relief of symptoms.	Subtotal gastrectomy. Healed gastric ulcer seen on microscopic section.
18	53	3 years of almost continuous epigastric discomfort or pain. Slight nausea. Pain xxx.	Clover leaf bulb.	14	Poor control. Pain persisted, xx.	500 mg. daily 14 days.	Complete control of symptoms. No pain.	Subtotal gastrectomy. Scarred bulb with narrow lumen, ulcer present.

TABLE I—*Continued*

Case	Age	Symptoms	X-Ray Findings	Standard Therapy Days	Result	T.A.C.	Result	Disposition Pathologic Findings
19	27	4½ years of almost continuous varying pain, nausea and vomiting. Pain xxx.	Clover leaf bulb.	20	Slight improvement in general comfort. Nausea and vomiting recurrent. Pain xx.	500 mg. 2 ×d. at intervals over 90 day period.	Complete relief as long as TAC maintained. Return of symptoms when TAC withheld 3–4 days.	Subtotal gastrectomy. Indurated duodenal ulcer.
20	26	No recurrences. Initial 4 months of pain. Later nausea and vomiting. Pain xx.	Irregular and tender bulb.	20	No improvement. Standard treatment prolonged because of absence of chronicity.	500 mg. 2 ×d. for 60 days.	Complete control of symptoms, no pain.	Discharged as arrested.
21	54	10 years of recurrent pain, nausea and vomiting. Perforation repaired six months ago. Pain xx.	Duodenal ulcer. 60% gastric retention in 5 hours.	16	Improved to point where emergency leave granted. Returned in two months with exacerbation and very severe pain xxxx.	500 mg. 2 ×d. for 8 days.	Complete control of symptoms without necessity of previous nightly aspiration of stomach. No pain.	Subtotal gastrectomy. Duodenal ulcer with deep fibrosis and external scarring.
22	53	30 years of recurrent pain, nausea and vomiting, usually in Spring and Fall. Pain xxx.	Clover leaf bulb.	28	These four weeks at private hospital before transfer here. No history of improvement during this period.	500 mg. 2 ×d. for 4 days.	Immediate relief of symptoms. No pain.	Subtotal gastrectomy. Chronic duodenal ulcer with scarring.
23	49	15 years of recurrent pain, nausea and vomiting. Rapid worsening before admission. Pain xxx.	Deformed bulb with 60% gastric retention in 5 hours.	3	No improvement noted.	500 mg. 2 ×d. for 10 days (added continuous gastric suction first 48 hours).	Pain completely relieved. Reduction in retention. (See text.)	Subtotal gastrectomy and abdominal vagotomy. Marked duodenal deformity and contracture. Duodenal ulcer.
24	39	Three years of recurrent epigastric pain or burning. Occasional mild nausea over this period. Pain xx.	Hyperperistalsis. Ulcer crater duodenal bulb.	0	—	500 mg. 2 ×d. for 14 days.	Complete control of symptoms. No pain.	Given 30 day leave, asymptomatic and negative x-ray on return.
25	28	6 months of recurrent epigastric pain with nausea. Occasional vomiting. Hospitalized twice before during this period. Pain xx.	Irregular and spastic bulb with tenderness.	0	—	500 mg. 2 ×day, 20 days.	Complete control of symptoms. No pain.	Discharged as arrested.
26	41	Slowly increasing recurrence of epigastric discomfort over 17 years. Frequent hospitalization. Nausea, vomiting, pain xxxx.	Ulcer crater in pyloric canal.	0	—	500 mg. one time on admission. (Pt. refused further "hypos.")	Relief of pain for 12 hours, then slow response to standard treatment.	Subtotal gastrectomy and abdominal vagotomy. Deep, punched out, pyloric ulcer.
27	57	10 years of recurrent epigastric pain. Admitted with hematemesis. Marked emotional instability. Pain xxx.	Spastic and deformed duodenal bulb.	0	—	1,000 mg. at admission. (Pt. adverse to hypodermic medication of any kind, refused further TAC.)	Relief from pain for 18 hours. Then slow response to standard treatment.	Discharged arrested. Pt. would not consider surgery.

Except for the fact that no pain impulses are transmitted by vagal afferent fibers, little is known of their function. Afferent pain stimuli are carried by fibers coursing with the splanchnic sympathetics. These have no ganglionic synapse and are anatomically and pharmacologically similar to peripheral sensory nerves. Perception of gastro-duodenal pain is lost when splanchnic sympathetics are severed, or when spinal anesthesia reaches the level of T6.[12] Such perception of pain is not lost when the vagus is cut.[13] Parasympathetic or vagal efferent impulses are predominantly motor and stimulate motility of and secretion within the stomach. Sympathetic efferent fibers predominantly inhibit motility and secretion.

Palmer [9] is a proponent of the concept that the pain of peptic ulcer arises directly from irritation of the ulcer base by gastric acid. The more generally held opinion is that ulcer pain arises more immediately from disturbances of the motor mechanism of the stomach and duodenum.[10] The well-known relief of ulcer discomfort when gastric acidity is reduced leaves no doubt as to the existence of some relationship between acid, ulcer and pain. This relationship need not depend upon primary nerve end-organ reception of pain stimulus within the ulcer. That it does not would seem to follow the observation of Smith et al.[12] of active peptic ulcer immediately following vagotomy with splanchnic sympathetics intact. They found that introduction of excess acid into the stomach in such instance failed to induce pain. It does not seem logical that the rapid relief of pain of ulcer following administration of TAC could result primarily from an equally rapid reduction in acidity, either by reduced secretion or reflux of alkaline duodenal contents.

We wish to offer an hypothesis of the mechanism of the pain of peptic ulcer which could reconcile divergent views: Chemical irritation of an ulcer crater produces local reflex spasm proximate to the site of ulceration. Motility or hypermotility of the stomach forces viscal contents against the partial obstruction of the site of spasm. Distention of the viscus (ordinarily the distal portion of the stomach) proximal to the obstruction affords the immediate origin of pain. This seems to us in accord with the consistent physiologic observation that distention is the sole adequate stimulus to visceral pain.[11]

In effect, a transient pharmacologic section or blockade of the vagus is accomplished when TAC is administered. Mimicking vagotomy, gastric motility is halted, spasm is relieved, distention behind obstruction cannot persist and pain is lost. With the fluoroscope and barium meal we have also observed the striking similarity between the inactive stomach following administration of TAC and that following vagotomy. Lyons et al.[3] and Brown, Posey, and Gambill [6] found a partial reduction in free gastric hydrochloric acid for a few hours after the administration of TAC. We have also observed this. Reduction in gastric acidity has been observed following vagotomy.[12, 14] The similarity of the effects of TAC and vagotomy is again notable.

This report demonstrates the usefulness of TAC as an agent for relief of the severe pain of peptic ulcer. In the use of the drug no side reactions of sufficient degree to be troublesome were encountered. Slight blurring of vision, slight lowering of supine blood pressure, and absence of perspiration were consistently present, and varied in duration from one to two hours. Marked postural hypotension rarely lasted over 30 minutes, and the erect position could be safely resumed in one hour. The majority of patients noticed some discomfort at the site of the injection, but felt it insignificant in relation to the relief of ulcer pain. Two rather neurotic patients refused further medication because of this discomfort. Incorporation of 0.5 to 1 per cent novocaine with the solution of TAC will materially reduce pain at the site of injection when troublesome.

Nineteen of our 27 cases were treated in preparation for surgery. TAC was given to relieve pain, and its use was incidental to presurgical care. In these, and in eight cases not subjected to surgery, duration of administration of the drug was widely varied. No correlation of the effect of TAC upon medical healing of peptic ulcer is warranted. However, the immediate and maintainable relief of pain obviously promotes the rest of the patient, and permits the therapist to pursue other efforts to healing of ulcer with greater facility. We believe that further studies of the contribution which TAC might make to the medical management of peptic ulcer are warranted.

Conclusion

1. Tetraethyl ammonium chloride, administered intramuscularly in dosage of 500 mg., consistently relieved severe pain of peptic ulcer in 27 cases.
2. An explanation of the mechanism of this relief of pain is offered.
3. Further investigation of the use of tetraethyl ammonium chloride in the treatment of peptic ulcer is warranted.

Addendum

In the two years intervening since preparation of this report, tetraethyl ammonium chloride has continued to serve the authors as a useful tool in the initial hospital therapy of peptic ulcer where pain is a factor. When pain is not relieved or relief is less than expected, we have learned to suspect the following explanations: penetration with local peritoneal irritation, organic pyloric obstruction, or marked exaggeration of symptoms of psychic origin.

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AURICULAR FLUTTER WITH COMPLETE HEART BLOCK *

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Recurrent reports in the literature concerning the rarity of auricular flutter with complete heart block and its probable etiology prompt us to report the following five cases. We believe that their histories and findings are of sufficient interest to warrant recording in order to clarify the significance of the above combination.

Case Reports

Case 1. A 64 year old World War I veteran complained of easy fatigability, dyspnea, precordial pain on effort, nocturia, and occasional ankle edema for the past five years. Despite these symptoms, he was able with some effort to continue his occupation as a book salesman. Past history was not relevant. *Pertinent physical findings:* peripheral arteries rigid and tortuous; moderate arteriosclerotic retinopathy; respiratory rate increased markedly on slight exertion; heart enlarged to the left on percussion; diffuse apical impulse palpated outside the mid-clavicular line; no thrills; heart sounds muffled; soft systolic murmur heard in the apical region. Both ventricular and pulse rate were recorded simultaneously as 38 per minute; rhythm was regular. Blood pressure 185/70 mm. Hg. All laboratory data within normal limits. Chest fluoroscopy revealed lung fields with accentuated vascular markings and "slow heart action"; the left ventricle was noted to be "of increased size"; calcification of the aortic arch was present. First electrocardiographic tracing on November 4, 1946, showed auricular flutter with what at first glance looked like a partial heart block with a seven to one or six to one ventricular response (figure 1A). However, closer scrutiny of the tracings revealed the presence of complete heart block. A month later, a repeat electrocardiogram showed the same rhythm abnormalities with the changes in pattern as noted in figure 1B. This patient had no Stokes-Adams phenomena, and we had no opportunity to try the effectiveness of various drugs on his heart block and flutter.

Case 2. A 75 year old white male entered the hospital because of weakness and swelling of the legs of five months' duration, dyspnea on effort, and dizzy spells. A history of recent diarrhea and bloody stools was also elicited. Past history was not relevant except for an admission to another hospital a year prior to this admission, where he was told he had a "slow heart." *Physical examination:* pale, comfortable, emaciated white male. Head, neck and chest showed nothing unusual. No thrills were palpated in the cardiac area, nor could the point of maximum impulse be localized. The heart was thought to be enlarged to the left by percussion; the sounds in the

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apical area were of good quality, with a short localized systolic murmur heard in this region. A_2 greater than P_2, rhythm regular; ventricular rate equaled pulse rate equaled 72 per minute. Blood pressure was 179/90 mm. Hg in both arms. Vessels of the arms and forearms were sclerotic and tortuous; those in the feet could not be palpated because of edema extending up to mid-abdomen. In the lower portion of the left side of the abdomen a small mass, approximately two and a half by four (2.5 × 4)

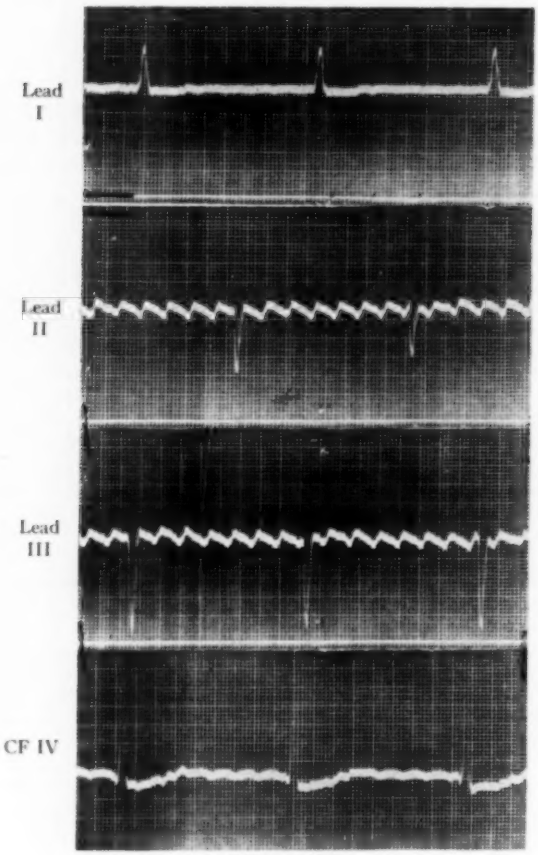

FIG. 1A. Case 1, age 64. November 4, 1946.

centimeters in diameter, was found, slightly tender on deep palpation. Proctoscopic and sigmoidoscopic examination failed to reveal any lesion, but fresh blood was noted on the wall of the rectum. The red cell count was 3,400,000 per cu. mm., and hemoglobin was 68 per cent. The urine always contained one to two plus albumin and occasional white cells and granular casts. Blood urea nitrogen was 30 mg. per cent. Teleroentgenogram of the chest showed an old fractured rib and clear lung

fields, while the heart was slightly enlarged to the left with a tortuous calcified aortic arch. The patient's course in the hospital is of interest: during the initial physical examination, his heart rate suddenly fell to 32 beats per minute without supervening Stokes-Adams syndrome. An electrocardiogram at this time revealed auricular flutter with four to one block. Subsequently the rate increased to 74 and again on numerous occasions it slowed down to about 32 beats per minute; however, on these occasions there was typical Stokes-Adams syndrome. Despite all types of medication, including digitalis, atropine and quinidine in adequate doses, the patient's ventricular rate tended to shift from 32 to approximately 74 beats per minute. These changes in rate were not always associated with Stokes-Adams syndrome. Electrocardiograms taken at frequent intervals (figure 2A) show the basic rhythm on these oc-

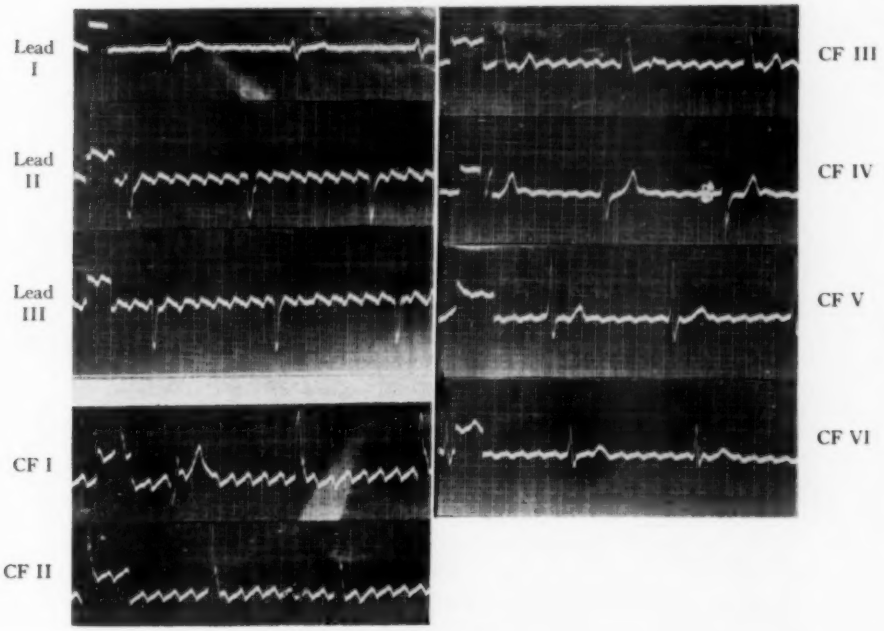

FIG. 1B. Case 1.

casions to be auricular flutter with a four to one or other ventricular regular response. On one occasion it was thought that a rapid flutter was present with a high degree of block, but more careful examination of this record (figure 2B) revealed that complete heart block was present and that the ventricular rate was independent of the flutter rate. On one occasion (figure 2C) regular sinus rhythm was present. These changes in rate or rhythm could not be correlated with medication given at that particular period. With the aid of mercurial diuretics, salt-poor diet, and digitalis, the patient became edema-free and fairly comfortable. The patient was transferred to the surgical service where a carcinoma of the sigmoid was found on operation. Two months after surgical exploration, the patient died. Autopsy permission was not obtained.

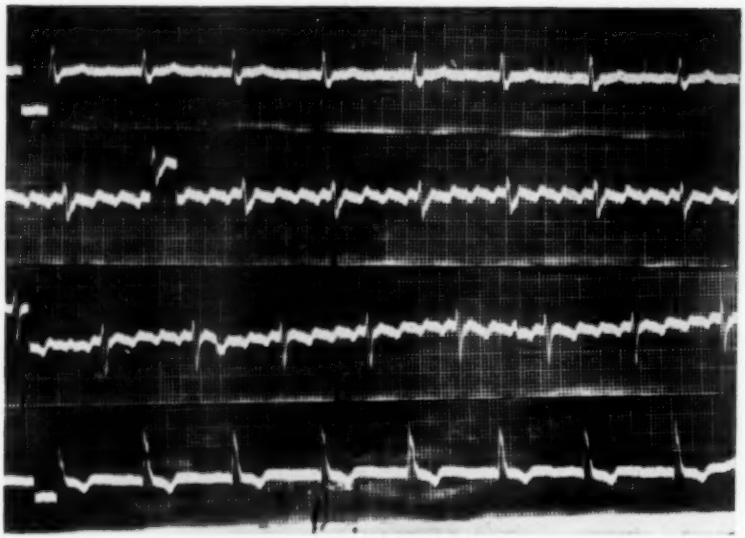

FIG. 2A. Case 2. January 5, 1947.

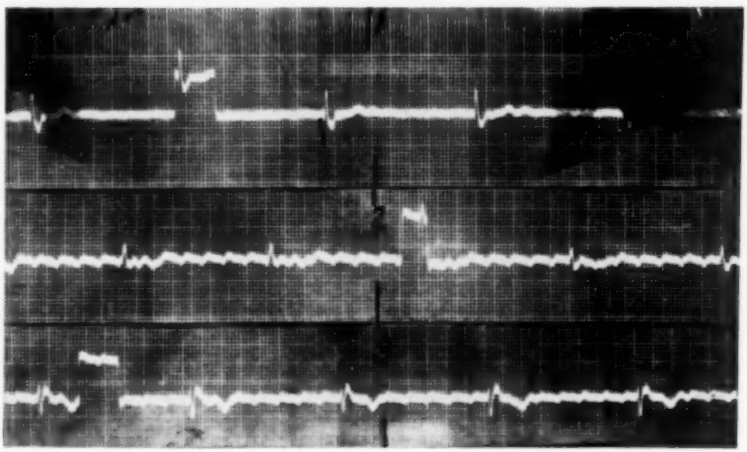

FIG. 2B. Case 2. January 16, 1947.

Case 3. A 72 year old white male was transferred to the hospital on March 18, 1943, from another hospital where he had had repeated admissions for arteriosclerotic and hypertensive heart disease associated with Stokes-Adams syndrome. Complete heart block with idioventricular rhythm was generally noted on those admissions. His present illness began three years ago. At that time he noticed ankle edema and

dyspnea on effort, and a year later he suffered the first "fainting spell." These occurred about twice monthly. Present clinical findings were related to the cardiovascular system. The heart was enlarged to the left, the point of maximum impulse 4 cm. beyond the midclavicular line. There were no thrills. At the apex a harsh systolic murmur was heard transmitted laterally and somewhat towards the base. A_2

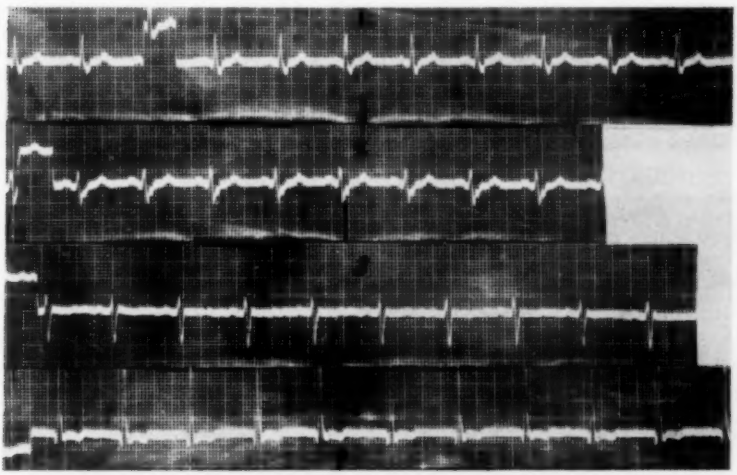

FIG. 2C. Case 2. January 23, 1947.

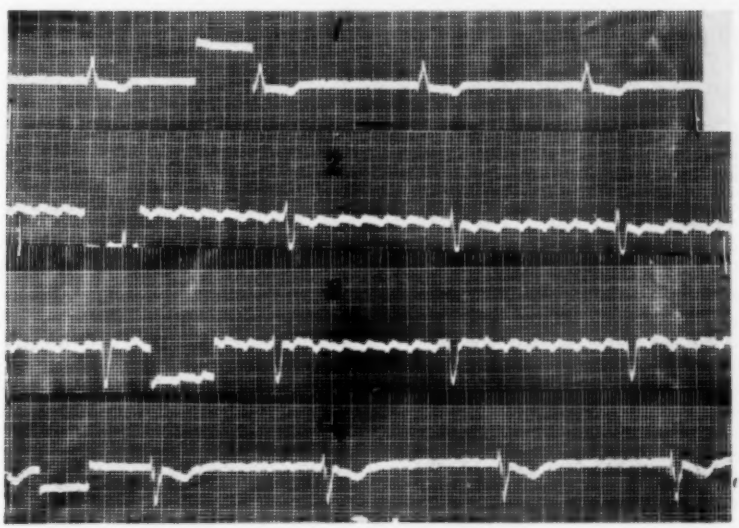

FIG. 3. Case 3. March 24, 1943.

was greater than P_R. Ventricular rate was 38 beats per minute, with regular rhythm. Blood pressure was 165/65 mm. Hg. Vessels of the arms and forearms were sclerotic and tortuous. *Laboratory data:* urine contained 2 plus albumin with occasional red blood cells and hyalin casts. Blood urea nitrogen varied from 19 to 33 mg. per cent. Phenolsulfonphthalein excretion test: 27 per cent in two hours. Teleroentgenogram of the chest showed some congestion of the lung bases; heart was enlarged both to the right and left; there was calcification of the aortic arch. Although information on previous hospitalizations and clinical findings foretold the finding of complete heart block on the electrocardiogram, we did not suspect the associated auricular flutter demonstrated in figure 3. Digitalis and quinidine had no effect on the cardiac rate or rhythm. Curiously, he had no recurrence of Stokes-Adams episodes. Seventeen months after admission, the patient died of a left-sided cerebral hemorrhage. Autopsy permission could not be obtained.

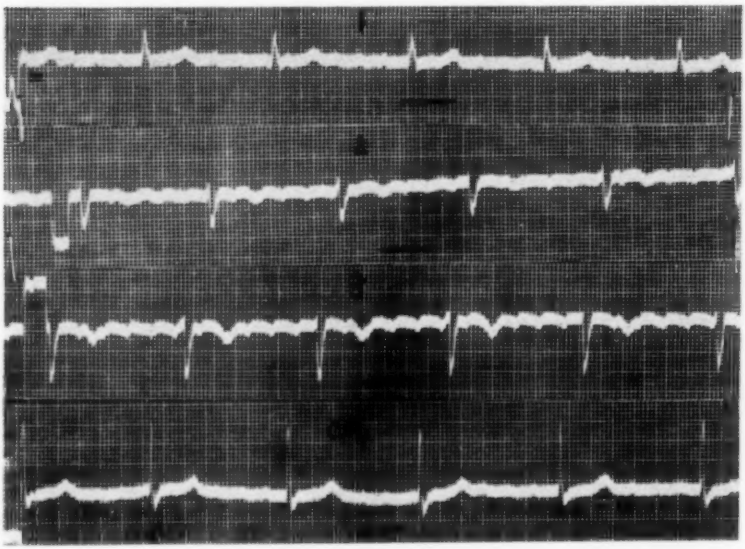

FIG. 4. Case 4. May 14, 1942.

Case 4. A 78 year old white male was admitted to the hospital in January, 1942, with complaints of chills, fever, and shortness of breath of two days' duration. Familial and past history were non-contributory. *Examination:* Patient slightly dyspneic and cyanotic; signs of a right lower lung lobe consolidation present. Cardiac impulse diffuse, no thrills; apical sounds of fair quality. The rhythm was totally irregular at 130 beats per minute. No pulse deficit was present. Blood pressure was 130/80 mm. Hg. Peripheral arteries were markedly sclerotic. Laboratory work of interest included a white cell count of 18,200. Of these, 82 per cent were polymorphonuclears. The sputum contained many gram positive diplococci. Roentgenogram of the chest showed consolidation of the right lower lobe, moderate enlargement of the heart, particularly of the left ventricle, and widened, tortuous aorta. The electrocardiogram was not remarkable, except for the auricular fibrillation.

With chemotherapy and digitalization, the patient made an uneventful recovery. After cessation of digitalis therapy over a two month interval the patient showed no signs of heart failure while ambulatory. Ten days after discharge, however, he was re-admitted for severe heart failure. Of significance on this admission, other than the usual signs of heart failure, was a systolic murmur in the apical region and an irregular ventricular rate of 48 beats per minute. The blood pressure on the second admission was 160/120 mm. Hg. The electrocardiogram (figure 4) showed auricular flutter and complete heart block. With the aid of digitalis and mercurial diuretics, compensation was regained and the patient was discharged.

Case 5. A 60 year old white male was admitted to the hospital on May 2, 1940, because of dyspnea on effort, swelling of the legs, and a residual right-sided hemiplegia resulting from a cerebrovascular accident in 1936. In 1939, because of repeated dizzy and fainting spells, he had been admitted to another hospital where the diagnosis of arteriosclerotic heart disease with complete heart block was made.

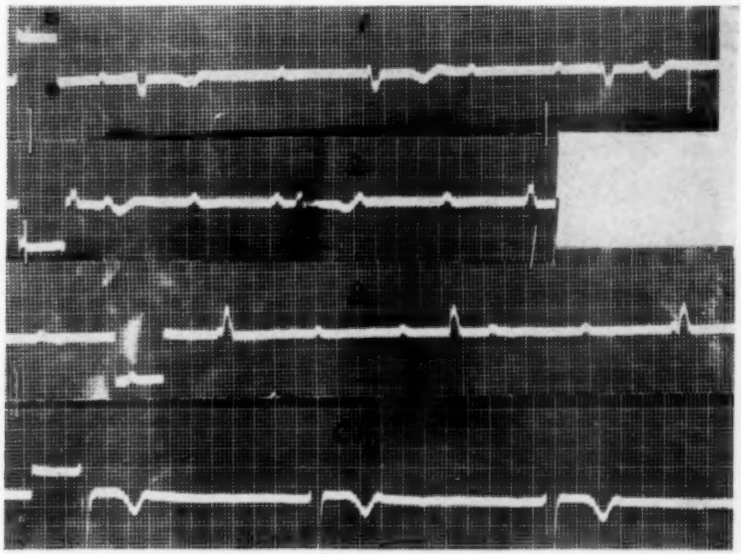

FIG. 5A. Case 5. May 3, 1940.

Pertinent physical findings, other than those of the residual right hemiplegia and peripheral arteriosclerosis, were related to the cardiovascular system. The heart was enlarged to the left; the point of maximum impulse was seen and felt in the sixth interspace outside of the midclavicular line. Sounds at the apex were of fair quality; the aortic second sound was accentuated. A harsh systolic murmur was heard over the entire precordium. The ventricular rate was 27 per minute; the rhythm was regular. The blood pressure was 200/70 mm. Hg. Liver was enlarged; dependent edema of the extremities was present. Laboratory data were of no significance. Teleroentgenogram of the chest disclosed congestion at both lung bases; the heart was reported as enlarged to the left and its configuration as consistent with that seen in hypertensive heart disease. Subsequent chest roentgen-rays confirmed the clinical impression of

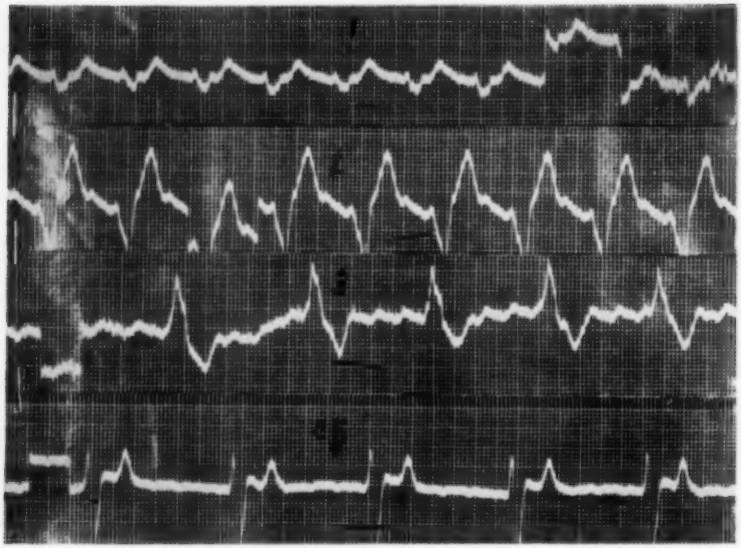

FIG. 5B. Case 5. July 8, 1940.

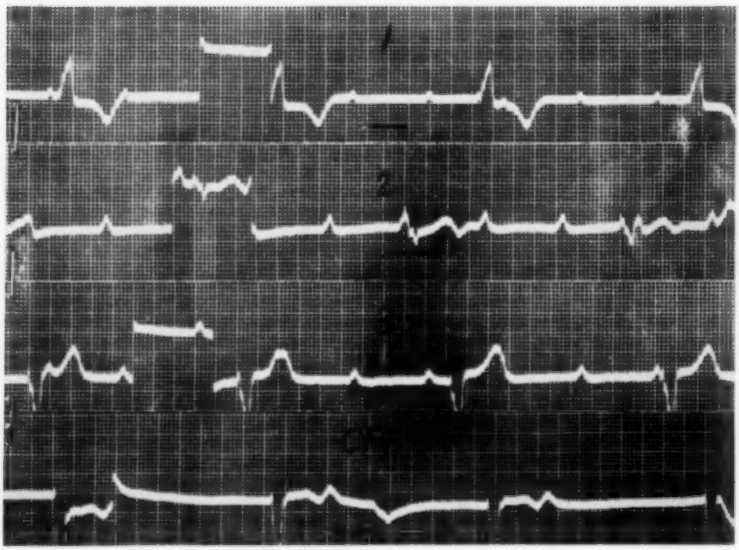

FIG. 5C. Case 5. May 14, 1941.

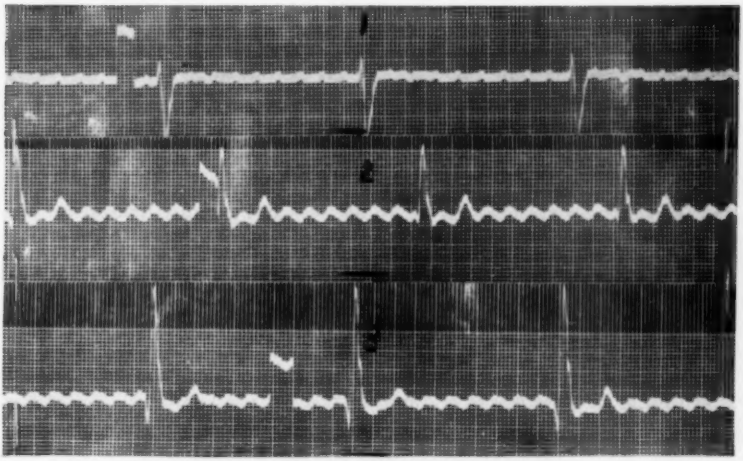

FIG. 5D. Case 5. February 24, 1942.

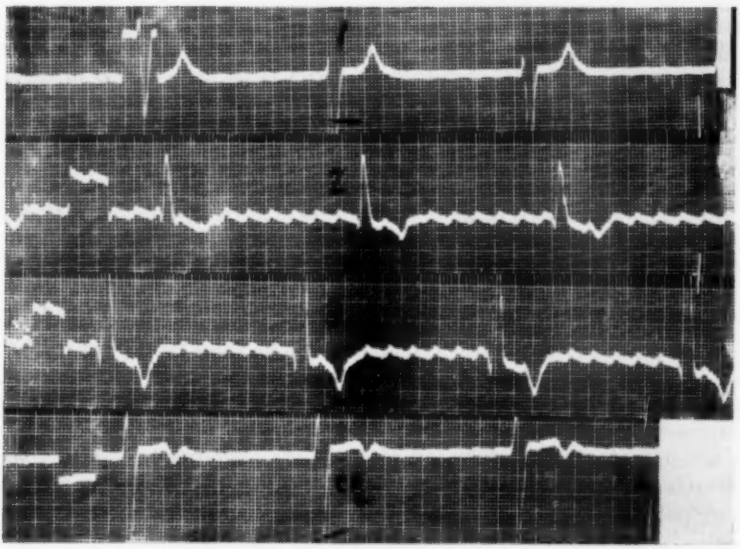

FIG. 5E. Case 5. January 25, 1945.

a gradually enlarging heart. The patient was followed in the hospital for a period of five years. Initially cardiac compensation was regained by the use of bed rest, salt-free diet, and mercurial diuretics. There was no change in his heart rate as seen in figure 5A. He had occasional bouts of dizziness and convulsive seizures associated with cardiac asystole. Because of recurrent cardiac failure while ambulatory,

the patient was digitalized. This therapy had no effect on his heart block. Ephedrine, barium chloride, atropine, quinidine, thyroxin, and paredrine were administered in high doses at different times through the years in an effort to influence the existing heart block but without avail. In 1943 the patient complained for the first time of precordial pain. During 1944 he was ambulatory and asymptomatic. Toward the end of 1945, dizzy spells became more frequent, and in February, 1946, he had a severe convulsive seizure associated with asystole, but the ventricular rate shortly returned to its usual level of 28 beats per minute. The patient died six hours after this episode. Permission for autopsy could not be obtained. Representative electrocardiograms over a five year period are seen in figure 5. Among these tracings, auricular flutter associated with complete heart block and idioventricular rhythm are shown in figures 5D and 5E.

Discussion

The first instance of auricular flutter associated with complete heart block was reported by Jolly and Ritchie [1] in 1910. Jourdonais and Mosenthal [2] (1937), in a survey of the literature reported a total of 29 cases, including their own. Willius [3] noted only one instance of this phenomenon in a review of 40,000 electrocardiograms. In a similar review of electrocardiograms, DiGregorio and Crawford [4] found two such tracings among 20,000 electrocardiograms at the Kings County Hospital. Thorborg [5] reported three cases, and recently Gray and Greenfield [6] (1944) and Pinto de Moura [7] (1946) each reported a case in a young adult. The latter author's report is of interest, since rheumatic heart disease was proved at necropsy.

Since this series of electrocardiograms was obtained mostly from elderly patients, it is our impression that auricular flutter associated with complete heart block is an abnormality most likely to be found in the later decades of life. The association of these phenomena is not incompatible with good cardiac function for several years, but it also may occur as a transitory finding in the progression of heart disease as exhibited in some of our cases. In a review of 12,948 + 1 * electrocardiograms, we found 1,655 with auricular fibrillation, 46 with auricular flutter, and 37 with complete heart block. Five had auricular fibrillation in combination with heart block, while the five cases reported here had auricular flutter in combination with heart block.

We believe this combination can no longer be regarded as a rarity. If electrocardiograms exhibiting auricular flutter with a high degree of block are scrutinized more carefully, examples of the abnormality will be found. The technic of Nyboer—using an esophageal lead—should be of value in questionable tracings.

While the clinical data in the literature are insufficient in too many instances to arrive at an accurate listing of etiologies, it is evident that arteriosclerotic heart disease was present in most cases; hypertensive heart disease seems to be a factor of only secondary importance. Rheumatic fever and syphilis apparently play only a minor rôle.

* This patient was seen in the Veteran's Administration R.O., Newark, N. J.

Summary

Five instances of auricular flutter associated with complete heart block are reported. All patients clinically exhibited severe generalized arteriosclerosis and at least two of them had arterial hypertension as well. The etiology and alleged rarity of this type of case are discussed.

Addendum

After completion of this paper, an article by Fenichel [8] appeared in which it was pointed out that "chronic auricular flutter" as such had been considered a rarity. Fenichel reports three cases in which auricular flutter had been observed for periods ranging from several months to over three years. He concludes that "chronic auricular flutter is not as rare as is generally believed." This statement is certainly borne out by our report. All our cases fall into the group of "chronic auricular flutter"; some of them have been observed for as long as five years.

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ERRORS IN DIAGNOSIS AND MANAGEMENT OF CANCER *

Part I

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THIS paper deals with errors in diagnosis and management of patients over varying periods of time in several hospital services. The correct diagnosis was finally achieved through the exercise of the viewpoint that nothing should be taken for granted. In reviewing these cases it became increasingly clear that the original error was one easily made, but that the continuation of that error was due to an acceptance of the original data without exploring their verity and completeness. Such errors can be avoided only by constant vigilance.

The educational aspects of these cases lie in the case histories themselves. It is felt that a reading of the details of the case reports as the patients were sent from hospital to hospital will indicate the errors and the methods of their detection.

These cases are presented with no thought of criticism of the previous care, or of the excellent institutions in which the patients received their original treatment. The first case which called our attention to the value of reviewing such a series of patients was one of our own.

The mass crowding of a group of patients labeled "terminal" in institutions designated for that kind of care carries a grave danger. The experience gathered from this group makes it seem reasonable to conclude that a fresh evaluation of any large group in mental institutions, in institutions for chronic care, or in homes for the incurably sick, would unearth a rewarding number of salvageable patients who can be returned to their normal place in society.

The vast majority of the patients treated in Montefiore Hospital suffer from prolonged illness or chronic disease. For purposes of this study we were especially interested in those with a diagnosis of advanced cancer. In a number of these patients, major errors in diagnosis or management were encountered. The case material can be divided into three major groups:

1. Patients admitted with the diagnosis of advanced cancer in its terminal stage, but who had no cancer.

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From the Divisions of Neoplastic Diseases and Surgery of Montefiore Hospital, New York City.
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2. Patients admitted with the diagnosis of advanced cancer in its terminal stage, but who had no evidence of local spread or metastases and were, therefore, candidates for curative therapy.

3. Patients who had cancer which was undiagnosed, despite a visible lesion of long duration.

At times the error was correctable, but in other instances the general deterioration of the patient prevented salvage. The material here presented emphasizes the diagnostic difficulties occasionally encountered and the need for discrimination in the interpretation of diagnostic evidence.

I. Advanced Cancer Was Diagnosed. None Was Present

This group consists of 11 patients. An outline of the case histories is presented in table 1.

Table 1

Advanced Cancer Diagnosed—None Present

Case Number	Diagnosis		Errors
	On Admission	Final	
1. (H. E.)	Carcinoma of rectosigmoid with pelvic metastasis.	Meningioma with cord compression.	No biopsy; inflammation mistaken for cancer at operation; diagnostic aids omitted.
2. (F. S.)	Carcinoma of breast with lymph node, pulmonary and osseous metastasis.	Osteomyelitis; bronchiectasis; extensive radiation necrosis; probable lues.	No biopsy.
3. (R. W.)	Carcinoma of stomach, extensive inoperable; secondary anemia.	Pernicious anemia, atrophic gastritis.	No surgical exploration; interpretation of roentgen-ray; diagnostic aid omitted.
4. (J. L.)	Carcinoma of rectosigmoid with pelvic metastasis.	Diverticulosis, diverticulitis.	No biopsy; inflammation mistaken for cancer at operation.
5. (I. S.)	Retroperitoneal tumor, inoperable.	Pyohydronephrosis.	No surgical exploration; diagnostic aid omitted.
6. (B. R.)	Papillary cancer of urinary bladder with bilateral obstruction and hydronephrosis.	Papilloma of bladder; ulcerative cystitis; ureteritis; pyelonephritis; hydroureter and hydronephrosis.	Histologic interpretation; no surgical re-exploration.
7. (M. K.)	Bronchogenic carcinoma with metastasis to skull and spine.	Intermittent atelectasis, osteoporosis, emphysema, bronchitis.	Roentgen-ray interpretation.
8. (E. F.)	Carcinoma of gall bladder; cirrhosis; ascites.	Pericholecystitis; cirrhosis of liver.	Inflammation mistaken for cancer at operation.
9. (L. F.)	Papillary adenocarcinoma of ovary with peritoneal carcinomatosis; mesenteric cyst.	Papillary serous cystadenoma of ovary.	Histologic interpretation; estimate of gross pathology; roentgen-ray interpretation.
10. (E. T.)	Papillary pseudomucinous cystadenocarcinoma of ovary. Peritoneal carcinomatosis.	Pseudomyxoma peritonei.	Histologic interpretation; estimate of gross pathology.
11. (J. N.)	Carcinoma of lung.	Interlobar empyema. Suppurative pneumonia.	Roentgen-ray interpretation. No surgical exploration. Diagnostic aid omitted.

Case 1. H. E. A 61 year old female was admitted to Montefiore Hospital in December, 1947, with a diagnosis of carcinoma of the rectosigmoid with multiple metastases and paraplegia.

Her first hospital admission was in August, 1942, because of "weight loss, bloody stools, weakness, increasing constipation, and cramp-like pain in the left lower ab-

dominal quadrant" of eight months' duration, which increased in severity so that intestinal obstruction was diagnosed. The surgeon described "a mass at the recto-sigmoid junction constricting the lumen and infiltrating into the retrocolic tissues, firmly bound down to the pelvis"; a colostomy was made. She was re-admitted in February, 1943, to the same hospital because of intense leg pain and inability to walk. Wasting of both legs (left more than right) was the only positive finding. She was discharged without additional workup in March, 1943. The leg pain was not relieved in the hospital and became unbearable, requiring increased doses of narcotics. In December, 1943, she developed bilateral paralysis and urinary incontinence. In June, 1944, this paraplegic patient was admitted to the same hospital for the third time. The only positive finding as recorded was "some edema around left ankle." Her abdominal pain was attributed to "probable metastasis." She was discharged unimproved. After six months of increasing use of narcotics she was admitted to a second hospital, her fourth hospitalization, where she remained only eight days. Her admission and discharge diagnoses at this hospital were the same: "Metastasis from carcinoma of colon and rectum; colostomy, 1942."

She was transferred directly to a third hospital, her fifth hospital admission. The summary received from this hospital repeats the history as already given, adding that there was an "increased extension of the malignancy into the surrounding pelvic viscera," and noting loss of bladder control and presence of sacral decubiti. She received "nursing care only." The diagnosis on admission there was "carcinoma of rectosigmoid with metastasis, and sciatic syndrome due to metastatic involvement." The final diagnosis, in April, 1945, was adenocarcinoma of the colon.

Throughout these five hospital admissions the operative diagnosis, unsupported by biopsy or endoscopic examination, remained unchanged. During the following one and one-half years she remained bedridden at home but maintained her general nutrition.

In December, 1947, she was admitted to Montefiore Hospital, her sixth hospitalization. After complete work-up, including investigation of the large bowel and rectum by endoscopy and barium studies, spinal fluid examination with manometrics and myelography, a benign extra-medullary, intradural tumor, extending from T–8 to T–7, markedly compressing and distorting the cord, was removed.

The microscopic diagnosis was psammomatous meningioma. Although some recovery from the paraplegic status occurred, the patient died one year later because of the long-standing cord compression and chronic decubitus. An incidental finding was carcinoma of the left breast with spread to the left axillary lymph nodes. Radical mastectomy was performed. Postmortem examination showed no evidence of residual or metastatic malignancy.

Symptoms simulating intestinal obstruction, secondary to spinal cord compression, are well known. The pitfalls of surgical judgment on exploration without tissue examination and acceptance of such erroneous judgments by succeeding physicians throughout five and one-half years are well illustrated by this case. Simultaneous digital examination of the distal colonic loop and rectum, as well as barium studies, would have confirmed the absence of malignant disease in the pelvis.

Case 2. F. S. A 62 year old female was admitted to our hospital in March, 1946, with a diagnosis of generalized carcinomatosis secondary to breast cancer. The important physical findings on admission are illustrated in figures 1 and 2. As can be seen from figure 1, the entire right half of the face and neck was covered with a brownish, pigmented, thickened skin extensively distorted and scarred. There were numerous fistulous openings present, oozing greenish purulent material, some covered

with crust. The lower half of the right concha is missing. Figure 2 shows several rather shallow ulcers surrounded by an erythematous border with central apertures, which exuded thick greenish pus and, on probing, appeared to originate in the bony structures.

This patient's illness began in June, 1941, five years earlier, with swelling of the right side of the face. A painless soft tissue swelling in the area of the ramus of the right mandible was found. Roentgen-ray of the mandible was negative. At the same time a stony hard 3 cm. mass in the right breast with dimpling of the nipple and a

FIG. 1. *Case 2*, F. S. Extensive scarring of face, neck, destruction of auricle, discharging face lesions. Radiation damage.

lymph node in the right axilla was described. In July, 1941, the neck mass was biopsied and the pathologic diagnosis was chronic cervical lymphadenitis. Two days later, without further biopsy of the breast, the patient was discharged with a final diagnosis of carcinoma of the right breast with chronic cervical lymphadenitis. She was referred for x-radiation therapy directed to the breast mass and to the right side of the face and neck.

She was well for two years. She then noted a breaking down of the skin of the face, with swelling and purulent discharge, and temporary right amblyopia. The

FIG. 2. *Case 2*, F. S. Osteomyelitic lesions of leg.

suppurative skin lesion failed to respond to local therapy. The wall of the lesion was biopsied and some of the suppurating areas opened and drained. The histologic examination showed "granulation tissue." Facial palsy resulted from this procedure. She spent almost two years in a convalescent home and was admitted to a second hospital, where the same findings were noted. However, on roentgen-ray examination, "metastatic disease of both lung fields and a left pleural effusion" were found. In the final sentence, it was stated that "there is no indication for further radiation therapy."

On admission to Montefiore Hospital in March, 1946, this cachectic patient had atrophic breasts with evidence of radiation pigmentation over the right breast; no masses were present. The chest findings previously interpreted as metastases were suggestive of pulmonary emphysema, fibrosis, and bronchiectasis. Roentgen-ray showed irregular stringy and nodular infiltrations with elevation and flattening of the diaphragm in the basal region of both lungs. The patient brought up copious amounts of thick greenish sputum, negative for tubercle bacilli, molds, or fungi. Roentgenograms of the right leg showed increased calcification of the lateral condyle of the tibia, with periosteal thickening of the tibia and fibula.

Attempts to find tubercle bacilli or fungi in the exudates failed. Only non-specific microörganisms were recovered. The blood serology was, on repeated occasions, strongly positive. Spinal fluid was negative. There was no history of syphilitic infection, primary or secondary.

A biopsy taken at the border of the ulcerated leg lesions revealed only "chronic and acute inflammation of the skin." The patient was treated with potassium iodide and penicillin by nebulization and parenteral administration, with temporary improvement. She died, however, of recurrent bronchopneumonia. Complete autopsy revealed no carcinoma but severe dermatitis of face and neck, probably secondary to radiotherapy, chronic osteomyelitis of the head of the right tibia with healed sinuses to the skin, purulent bronchitis with cylindrical bronchiectasis, and bilateral bronchopneumonia. There was no anatomical evidence of syphilis, either visceral or of the central nervous system.

A breast mass was diagnosed as cancer without biopsy. Once so diagnosed, without evidence of metastasis, surgery, the accepted treatment, should have been undertaken. Whether this patient had a breast cancer prior to radiotherapy it is impossible to state. At autopsy, five years after the onset, no trace of breast cancer or metastasis was found. The radiotherapy to the face and neck resulted in severe dermatitis, necrosis, secondary infection, and metastatic osteomyelitis of the tibia. Fibrosis and bronchiectasis of both lungs were mistaken for metastatic cancer, because five years earlier a diagnosis of breast cancer was made without biopsy. The nature of the cervical lymphadenitis which initiated the chain of diagnostic and therapeutic errors remains unclear. Syphilis probably played no rôle.

Case 3. R. W. A 64 year old female was transferred directly to Montefiore Hospital in August, 1943, from another hospital which submitted the information that the patient complained of anorexia and other gastrointestinal symptoms and a 60 pound weight loss. Four weeks of tingling, numbness and weakness in hands and feet and a one week history of eruption over abdomen and chest with severe itching. Three gastrointestinal series showed some infiltrative lesions of the distal two-thirds of the stomach. The patient was said to have a secondary anemia which responded to intramuscular liver extract. She was felt to be inoperable and was transferred to Montefiore Hospital for chronic care. Final diagnosis: carcinoma of stomach.

On admission to Montefiore Hospital in August, 1945, the only additional information obtained was that she had had a cholecystectomy eleven and one-half years before admission. The pertinent findings were obtained on neurologic examination, which revealed decreased deep tendon reflexes of the lower extremities bilaterally, bilateral Babinski sign, impaired position and vibration sense in both lower extremities, and decrease in pin prick sensation in the same area. These were interpreted as suggestive of posterior and lateral column involvement of the spinal cord with subacute combined degeneration. Hematologic examination, including marrow study, presented the characteristic picture of megaloblastosis seen in pernicious anemia. The patient was given liver extract injections and responded with a prompt rise in the reticulocytes and improvement of her hematologic status, together with improvement of her general condition, strength, weight and neurologic findings. Physiotherapy was given and the patient left the hospital much improved and in complete hematologic remission. Barium meal examination of the stomach showed findings indicative of atrophic gastritis with absence of gastric rugae. There was no definite evidence of a lesion in the gastric wall.

The patient was re-admitted to our hospital two years later with general debility, weight loss, and swelling of both lower extremities. The findings again were characteristic of pernicious anemia in relapse, with subacute combined degeneration of the cord. She again responded promptly to liver extract treatment. Repeated barium studies of the gastrointestinal tract confirmed our original impression of atrophic gastritis. There was a marked atrophic glossitis. Gastric analysis was refused. She was again discharged with normal blood status, much improved.

It is noteworthy that in the summary quoted earlier in this case history, a smooth infiltrative lesion of the distal two-thirds of the stomach was found on three consecutive gastrointestinal series. It is interesting to note that the neurologic findings were not described, although the history of tingling, numbness, and weakness was mentioned. The prompt response of a secondary anemia to intramuscular liver extract should have led to a more detailed investigation, since secondary anemias are ordinarily not responsive to liver extract treatment. A review of this case revealed that, although this patient had what appeared to be typical roentgen-ray findings of carcinoma of the stomach with severe anemia and general deterioration, the favorable response to liver therapy was overlooked and the patient sent to this hospital for terminal care. It is well known that gastric carcinoma developing in pernicious anemia occurs relatively frequently and is at times difficult to diagnose. Pernicious anemia mistaken for gastric carcinoma is probably less frequent.

Case 4. J. L. In May, 1944, a 54 year old white married male was transferred to our hospital with the information that he first consulted a clinic in August, 1942, complaining of weight loss and anorexia of six months' duration, and cramp-like lower abdominal pain of three weeks' duration. Barium enema revealed an obstructive lesion at the rectosigmoid. In October, 1942, the patient was admitted for exploratory laparotomy. A tumor measuring well over 15 cm. in length and 8 to 10 cm. in diameter was found in the rectosigmoid. Gallstones were also noted, and there was an extensive disease in the pelvis. No liver metastasis was noted. A palliative transverse colostomy was constructed. In April, 1943, and March, 1944, the patient was given a cycle of radiation therapy to the pelvic area. He had been seen at monthly intervals in the clinic until April, 1944. For the past few months the

patient was unable to irrigate the colostomy satisfactorily. "This was considered a result of the patient's emotional instability."

On admission to Montefiore Hospital in May, 1944, the history included a statement that he had been operated upon for acute appendicitis 22 years ago, at which time diverticula were also found. The same statement had been made at the hospital of origin. On physical examination the only significant finding was a palpable fixed tumor in the left lower abdomen, best felt by digital examination through the distal colostomy loop. The patient was in good general condition and had maintained his weight throughout the previous two years. Laboratory tests were essentially within normal limits. In spite of the paucity of evidence, the weight of the information transmitted to us was such that the diagnosis of the admitting physician read: "Carcinoma of the sigmoid with metastasis to the pelvis." After the workup was completed and data became available for a final evaluation, a note dated June 12, 1944, read as follows: "Exploration at previous hospital where fixed sigmoid tumor was found to be not resectable. Palliative colostomy performed. Abdominal and rectal examination negative. Palpation through colostomy opening reveals a fixed tumor of the sigmoid above the pelvic brim. Custodial care."

A critical analysis of the data reveals no tissue biopsy to establish the diagnosis of cancer. As for its resectability, the operative note reveals that conspicuous adhesions surrounding the tumor and attached to the loop of the bowel and even across the abdomen to the cecum were present. The entire structure is *movable* but extends into the pelvic cavity. "In order to resect the tumor it would have been necessary to sacrifice the superior hemorrhoidal artery."

The classification of the patient as a custodial case was, however, correct, because even after one year's stay at Montefiore Hospital the findings were essentially unchanged. During this period occasional fever with chills interfered with the patient's custodial life. These episodes were interpreted as urinary tract infection secondary to the invasion of the bladder by the malignant tumor.

In September, 1945, it was again noted that there was no local extension of the disease and no evidence of distant metastases, and that the patient had maintained his weight throughout the year. A complete re-investigation of his condition was carried out. The only pertinent findings were obtained on sigmoidoscopy and barium enema: seven and one-half inches from the colostomy opening the instrument met a grayish constricting tissue which was biopsied and was negative for neoplasm. The barium enema filled the rectum and the normal lower sigmoid colon until it met with complete obstruction.

In October, 1945, three years after the first operation, a resection of the inflammatory tumor with primary end-to-end anastomosis was carried out. The gross examination of the removed bowel—14 cm. long and 4 cm. in circumference—revealed characteristic diverticulosis and diverticulitis. Microscopic examination confirmed the gross findings. In the ensuing one and one-half years, in order to obtain restoration of normal bowel continuity, the patient submitted to five additional procedures: (1) a new colostomy proximal to an internal fistula; (2) closure of the original colostomy; (3) transection and revision of the new colostomy; (4) laparotomy for division of ileo-sigmoidal fistula and, finally, in April, 1947, (5) closure of colostomy.

On his last follow-up visit in July, 1950, he had no complaints, had regained his full weight, was working steadily, and was able to support his family for the first time in over seven years.

The pitfalls in the differential diagnosis of diverticulitis and cancer of the large bowel are well demonstrated. The danger of the "cancer label" without tissue diagnosis is well illustrated in this case.

Case 5. I. S. This 76 year old male was admitted to Montefiore Hospital for terminal care in June, 1946, with a history of weakness, weight loss, constipation, and vomiting. For these complaints he had been admitted to another hospital, two months earlier, with a tentative diagnosis of carcinoma of the ascending colon with partial intestinal obstruction. Roentgen-ray examination did not confirm this opinion. The positive findings in this case were: albuminuria 3 plus; numerous white blood cells per high power field; non-protein nitrogen of 50 mg. per 100 c.c. Although on physical examination on admission a large hard mass was felt in the right flank of the abdomen, no further attempts were made to clarify the etiology of this mass.

On admission to Montefiore Hospital in June, 1946, the same mass was palpated, and albuminuria and pyuria were found. There was a severe anemia with leukocytosis up to 14,000. On cystoscopy a large quantity of coagulated pus was found in the bladder and, after continuous irrigation, the ureters were visualized and catheterized. Thick, foul, purulent material was aspirated from the right renal pelvis, and retrograde pyelogram was completed, demonstrating a large hydronephrotic kidney (figure 3).

On August 6, approximately four months after his first hospital admission, a right nephrectomy was performed. At operation the kidney was found to contain 600 c.c. of thick, foul-smelling pus. After aspiration of the pus the kidney weighed 570 gm. The parenchyma was thinned out so that the large kidney represented mainly a sac. Despite his age and general condition, the patient made an uneventful recovery from the operation and was discharged improved.

Correction of the diagnosis in this instance and salvage of the patient were made with relative ease because of the huge palpable mass in the right flank, together with pyuria, albuminuria, anemia, and leukocytosis. In spite of the patient's age and the long-standing damage to the organism by the presence of such an extensive infection, nephrectomy was still possible and rewarding in that the patient left the hospital without signs of disease and with the assurance that he had no malignancy.

Case 6. B. R. This 68 year old male died in this hospital in October, 1945, of an ascending urinary tract infection, uremia, and terminal bronchopneumonia. His illness began in November, 1944, with dysuria and hematuria of progressive and increasing severity. Two weeks after the onset of his symptoms he was admitted to a hospital where a bladder tumor was visualized on cystoscopy and a specimen removed for biopsy. In December, 1944, fulguration of the tumor was performed through a suprapubic cystotomy. The operative report states that " a flat sheet of carcinomatous growth was seen extending from the bladder neck involving the trigone, the base of the bladder neck and the lateral wall. The ureteral orifices are embedded in this mass and cannot be visualized." A piece was taken for biopsy and then the entire growth was fulgurated. A bilateral hydronephrosis was found on roentgen examination. The surgical specimen was reported as papillary carcinoma of the bladder. The patient was discharged 20 days after surgery. He was probably seen occasionally in the out-patient department, although no statement is made in the report sent to our hospital.

His condition became gradually worse and necessitated a second admission to another hospital in April, 1945, where he stayed for six weeks. In response to a request for information, the second hospital submitted the following: "Diagnoses: carcinoma of the bladder. Cystoscopy revealed extensive involvement of the right wall, posterior wall on the right and in the middle at the bladder neck." No statement was made as to ureteral blocking, kidney function, or therapy given or contemplated.

When this patient was subsequently admitted to Montefiore Hospital (the third hospital) in August, 1946, he showed marked evidence of wasting, occasionally spiking temperature, and severe upper and lower urinary tract infection. There was an abscess near the suprapubic tube which had to be incised and drained. Blood urea nitrogen was elevated, the urea clearance being excessively low. A specimen sub-

FIG. 3. *Case 5,* I. S. Retrograde pyelogram.

mitted for biopsy was reported as benign papilloma. This patient deteriorated steadily and died in uremia with blood urea nitrogen at 75 mg. per cent.

At autopsy a broad flat papilloma involving the bladder neck and extending to the right posterior wall was found. The ureteral orifices were found to open a few millimeters above the papilloma. Severe ulcerative cystitis and ureteritis were present and bilateral pyelonephritis with dilatation of both ureters and renal pelves.

It is not within the scope of this presentation to discuss the difficulties encountered in the histologic diagnosis of bladder papillomas, benign or malignant. This has been sufficiently documented in the literature. It is known that the evaluation of the endoscopic picture or of the histologic examination of small pieces of tissue removed for biopsy is very trying. But once the diagnosis of bladder carcinoma, obstructing both the inflow and outflow pathways, is made, there are a number of therapeutic measures available to treat the tumor and protect the kidney. In a tumor notorious for its capacity for frequent regrowths after fulguration, careful repeated follow-up study is essential. Repeated fulguration, intravesical radium treatment, roentgen-ray irradiation, and surgery are measures which can be used to relieve ureteral obstruction. Apparently none of these was done persistently for this patient. This is the more distressing as this patient actually did not have bladder cancer.

Case 7. M. K. A 64 year old male was admitted to this hospital in December, 1946, for terminal care with a diagnosis of carcinomatosis, probably secondary to bronchogenic cancer. This diagnosis was based upon the findings obtained in another hospital, which stated that he was admitted on October 13, 1946, complaining of severe sharp low back pain of four days' duration which had begun, more mildly, one month earlier. While bending down he experienced exquisite pain in the left ilium which persisted and was aggravated by any motion. Two years previously the patient was on the Chest Service for shortness of breath and cough. He refused bronchoscopy. He was acutely ill and in great pain. The essential findings were in the chest, which showed increased P–A diameter, dragging on the right, dullness at the right base with diminished breath sounds and fine medium moist râles, scoliosis, and limitation of motion of upper lumbar spine with muscle spasticity. Positive Lasègue sign on the left was found.

Roentgen-rays revealed irregular pneumonitis in the lower third of the right lung and extensive interstitial changes with fibrosis at the root. In October, 1946, considerable compression of the body of the fourth lumbar vertebra was found and a metastatic process was considered. A few days later extreme compression of the body of the fourth lumbar vertebra with compression of the right side of the body of the third lumbar vertebra, considered as probably due to a metastatic process, was found. The same day, metastatic lesions in the skull were discovered. On bronchoscopy, considerable mucopurulent secretion, with a foul odor, was found in the right main bronchus arising from the lumina of the right middle and lower lobe bronchi. There was complete stenosis of the right middle lobe bronchus, which bled freely and from which a biopsy was obtained. Tumor was not found in the tissue submitted. "Despite the negative biopsy report it is felt that the x-rays are conclusive for carcinoma."

After admission to Montefiore Hospital in December, 1946, extensive work-up, including bronchoscopy, bronchograms, biopsy of endobronchial mass, bacteriologic and chemical studies, studies of cardiorespiratory function, and osseous roentgen-ray survey, was done. The clue to this case was the advanced generalized osteoporosis leading to a biconcave deformity of all the lumbar vertebrae, especially the first, third, and fourth, producing the effect of fish vertebrae, accompanied by a marked ballooning of the intervertebral disks. The "skull metastases" were also interpreted as osteoporosis. The endobronchial "tumor" was identified as redundant mucosa which partially occluded the mouth of the right middle lobe during expiration. Closure of this bronchus with pneumonitis accounted for the recurrent attacks of pulmonary disease.

Once this process was understood and the social history obtained (revealing semi-starvation because of low economic status), treatment consisting of improved dietary regime and use of antibiotics parenterally and by nebulization brought considerable and quick relief. The patient was discharged on May 11, 1947, having regained strength and weight and being asymptomatic. Our final diagnoses were: emphysema, suppurative bronchitis, intermittent occlusion of right bronchus with recurrent pneumonitis, and advanced osteoporosis.

Case 8. E. F. A 74 year old female, mildly diabetic, had been in otherwise perfect health until the early part of 1946, when she began to have weakness, mild upper abdominal pain, distention, and a 21 pound weight gain. In June, 1946, a laparotomy was performed for probable chronic cholecystic disease. A "stony, hard, enlarged gall bladder, adherent to the hepatic flexure," was found. The liver was reported to be enlarged and cirrhotic; ascitic fluid was present. A Talma procedure was performed. The pathologic diagnosis was "no malignant cells in abdominal fluid." Clinical diagnosis on discharge was carcinoma of gall bladder.

This patient was admitted twice to a second hospital for abdominal paracentesis and then referred to us for management with a final diagnosis of carcinoma of gall bladder with metastasis to the liver.

When admitted to Montefiore Hospital in May, 1947, she was in fair general condition, with slight icterus of the skin and sclerae, ascites, edema of lower abdominal wall and both legs, a circumscribed tumor (proved to be an organized hematoma) in the anterior abdominal wall, and a stony hard mass, 10 cm. in diameter, in the right upper quadrant which moved on respiration.

The laboratory tests yielded the following information: The gall bladder was not visualized after Graham-Cole test. No stones were seen in that region. The descending duodenum on barium study showed evidence of extrinsic pressure on the right, making its contour concave but with a normal mucosal pattern. Blood count was normal. Icteric index was 11 and total protein and A/G ratio were normal, as were thymol turbidity, cephalin flocculation, and alkaline phosphatase. Hippuric acid test was normal once, and once was impaired. The bromsulfalein test showed marked retention. Urines and stools were essentially normal. Repeated paracenteses yielded clear fluid in which "no tumor cells were found." There was no external evidence of collateral circulation and no esophageal varices. The patient died during her second admission here, one year after exploration, of a terminal bronchopneumonia. On autopsy a moderately distended, quite tense gall bladder with numerous adhesions to duodenum and transverse colon was found. Its wall and mucosa were normal. The extra-hepatic biliary ducts were distended though patent throughout. There was hepatic and pancreatic cirrhosis.

It may be assumed that this patient had at one time an upper abdominal inflammatory process causing marked adhesions and thereby distention of the gall bladder, producing a tumor which could easily be mistaken for a gall bladder cancer on exploration. An acute onset of decompensation of portal cirrhosis of long standing is frequently observed. The lack of evidence of major liver function impairment in hepatic cirrhosis with regeneration of sufficient functioning liver tissue is notorious.

Whereas errors in the differential diagnosis of liver cirrhosis and primary diffuse liver cancer are common, a pericholecystitis is rarely mistaken for cirrhosis or gall bladder cancer. Without histologic proof, and with

atypical gross findings, a diagnosis should be withheld rather than a cancer label erroneously attached.

Case 9. L. F. This 64 year old female was admitted to Montefiore Hospital in June, 1943, as a terminal cancer patient referred for palliative radiotherapy. Her illness began in December, 1942, signaled by the onset of weakness, nervousness, abdominal distention, constipation, and an enlarged mass in the left lower quadrant of the abdomen. There had been no melena, chills or fever. For these complaints she was admitted in February, 1943, to a hospital where examination revealed a smooth cystic nodular mass arising in the left pelvis and occupying most of the left lower quadrant. The mass was movable and appeared to be attached to the uterus. She was explored surgically in February, 1943. On exploration many peritoneal implants on visceral peritoneum and a large retroperitoneal cyst dissecting into the mesocolon were seen. The ovaries were palpated and the left ovary was abnormal and had a granular feeling. Biopsy was taken. The mesenteric cyst was opened and fluid was aspirated. The condition was deemed inoperable and the abdomen was closed. The pathologic diagnosis was papillary adenocarcinoma, highly suggestive of ovarian origin. The discharge diagnosis was adenocarcinoma of the ovary, peritoneal carcinomatosis.

In June, 1943, on admission to Montefiore Hospital, a soft pelvic mass involving the uterus and both adnexae was felt. Radiotherapy was given and the patient was discharged two months later. Five months later, in February, 1944, she was readmitted because of the recurrence of "ascites," dyspnea, and vague digestive disturbance. Radiotherapy was again administered. Six months later it was noted that the mass had grown considerably. "Ascitic" fluid, pale, yellowish in color and containing no tumor cells, was removed. She was discharged, to be re-admitted in July, 1945, two and one-half years after the original laparotomy. The cause of admission was vaginal bleeding. A large mass was found occupying the entire lower half of the abdomen, and palliative surgery was agreed upon in order to remove as much tumor as possible to facilitate radiotherapy.

Exploratory operation was done in November, 1945, two years and nine months after her first hospitalization. The operative report follows: "There is a football sized cyst attached to the region of the left ovary. Small bowel is attached to the mass by adhesions. A panhysterectomy was done." The surgeon did not find peritoneal implants. The pathologic report was "papillary serous cystadenoma of the ovary," the cyst measuring 19 by 19 by 12 cm. This patient made an uneventful recovery postoperatively and has been well since discharge.

This patient became ill in December, 1942, and had four hospital admissions (a total of 21 months) in the following years for a serous cystadenoma of the ovary which was resectable three years later. Peritoneal carcinomatosis was not present. Ascites was not present. The fluid removed from the abdominal cavity was within the cyst wall. It is not unusual to mistake encapsulated fluid for ascites. It is, however, rare to have radiographic evidence of the presence of such an encapsulated fluid and still overlook it. On roentgen-ray examination of the abdomen one year prior to the surgical removal of the cyst a large ovoid mass was seen, filling out and apparently rising from the pelvis and extending into the abdominal cavity. Overlying its right upper border the calcified wall of a cystic mass, measuring 8 to 10 cm. in diameter and resting upon it, is plainly visible (figure 4). After removal of the support this mass is seen to have dropped downward

and to represent the calcified wall of a huge cystic gall bladder. Another calcified shadow, a gall stone, measuring 2 to 3 cm. in diameter, is seen on this film in the area of the neck of the gall bladder (figure 5).

*Case 10.** E. T. A 55 year old female was admitted to this hospital in January, 1941, with a diagnosis of papillary pseudomucinous cystadenocarcinoma of ovary. Her illness had begun 10 months previously, manifested by progressive enlargement of the abdomen for which she had been treated in three hospitals. She was admitted

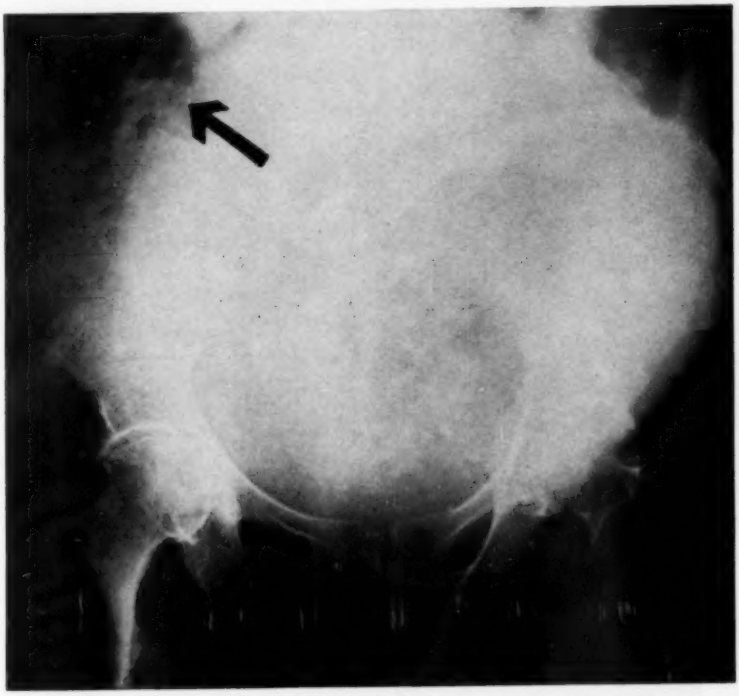

FIG. 4. *Case 9*, L. F. Flat film of abdomen showing large round density in lower abdomen and pelvis, surmounted by calcified gall bladder.

to the first hospital where paracentesis was performed, yielding gelatinous material the stroma of which suggested "pseudomyxomatous origin." The patient was transferred to a second hospital, where pelvic examination revealed a mass in the right fornix and in the right lower quadrant of the abdomen. An exploratory laparotomy was performed and, when the peritoneum was opened, an extremely large amount of thick jelly-like material escaped. There were large cystic masses occupying the entire pelvis, adherent to the bowel and to the lateral pelvic walls. There were innumerable

* This case is one of a group which was presented in a separate paper by Dr. E. D. Rosenfeld from the Division of Laboratories of this hospital in Arch. Path. **48**: 255, Sept. 1949.

implants, small, friable, and soft, in the omentum, bowel, and parietal peritoneum. A portion of the cyst wall was excised for biopsy. The specimen was insufficient for microscopic diagnosis, but on discharge the diagnosis was papillary pseudomucinous cystadenocarcinoma of ovary.

A third hospital to which the patient had been admitted stated that radiotherapy totalling 2,000 R had been given but was discontinued because of reaction.

FIG. 5. *Case 9*, L. F. Postoperative flat film showing gall bladder, calcified and enlarged, after removal of the supporting cyst. Another calcified shadow seen in the area of gall bladder neck.

She was admitted to Montefiore Hospital in January, 1941, seven months later. In the ensuing months at this hospital many paracenteses were done, some requiring suction to remove the thick gelatinous material which had accumulated rapidly in the abdomen. As much as 8,000 c.c. were removed at one sitting. Radiation therapy was administered and provided some noticeable improvement and added considerably

to the patient's comfort. Having been palliated by this treatment, she was discharged after a hospitalization of 10 months. The diagnosis at the hospital where surgery had been performed had been accepted by all concerned in spite of other information available, and the discharge diagnosis was cystadenocarcinoma of the ovary.

After discharge, the patient was followed in the clinic. There was slow but definite re-accumulation of intra-abdominal fluid and masses, for which many admissions were required. Each time, large amounts of gelatinous fluid were removed from the abdominal cavity. The speed of accumulation of the fluid is shown by the following: 13,700 c.c. were aspirated and six weeks later 11,300 c.c. were removed. Additional radiotherapy was given at intervals.

Finally, in early 1946, the patient was admitted to this hospital for the twenty-second time over a period of five years. It was only on this re-admission, six years after the onset of the disease, that enough doubt was expressed concerning the accuracy of the diagnosis and treatment to warrant re-exploration. Laparotomy was performed and a large cystic mass, grossly considered to be cystadenocarcinoma of the ovary, was removed. The postoperative course was relatively uneventful. The surgical specimen sent to the laboratory was described as being a large irregular mass of tumor measuring 27 by 14 by 7 cm. The nodularity of the tumor was produced by a large number of cystic spaces, filled with glairy greenish gelatinous fluid, which occupied the entire extent of the mass. The histologic diagnosis was pseudomucinous cystadenocarcinoma. She was discharged considerably improved, and was followed in the out-patient department. On April 24, 1947, one year postoperatively, a note was made that "the examination is essentially negative and the patient has no complaints."

Three months later the patient was re-admitted to Montefiore Hospital for her twenty-third and last hospitalization. Two days before she had had sudden onset of severe abdominal pain, nausea, anorexia, constipation, and fever. The pain began in the patient's right upper abdominal quadrant and radiated across the epigastrium to the left side and around to the back. It was severe and caused her to double up, requiring injections for relief. Her sleep was interrupted by the pain. Physical examination on admission revealed some nodularity of the abdominal wall, resistance to palpation throughout the abdomen, and mild generalized rebound tenderness. Peristalsis was normal and there was a mild distention and tympany. The admission diagnosis was partial intestinal obstruction. In the course of the next several hours the patient developed shock and signs of diffuse peritonitis, thought to be caused by a ruptured viscus. Her condition was too poor to allow exploratory surgery. Attempts to treat the shock failed and she died in July, 1947.

Autopsy revealed a ruptured mucocele of the appendix, with diffuse purulent peritonitis, and partial small intestinal obstruction, the result of kinking of the terminal ileum. There were pseudomyxomatous implants on the diaphragm and spleen.

The final diagnosis was pseudomyxoma peritonei of appendiceal origin. This patient died after an illness of a little over six years for which she had been hospitalized 26 times in four hospitals and had been explored surgically twice. The appendix was not inspected either time, in spite of the presence of gelatinous material once thought to be suggestive of pseudomyxoma peritonei.

Case 11. J. M. A 63 year old male was transferred to Montefiore Hospital in April, 1947, with the diagnosis of carcinoma of the right lung. He had entered another hospital in January of that year with the complaints of fever, cough, expectoration, and weakness, and had remained there for four months. We were informed that at first a suppurative pneumonia involving the right upper lobe of the

lung was suspected and that the patient had been treated with penicillin and sulfadiazine. His temperature, cough, and foul-smelling sputum receded. Following this treatment, however, a consolidation within the affected lobe persisted. In view of the patient's rapid deterioration, the reappearance of copious sputum shortly after the discontinuance of the antibiotics, the persistence of the consolidation, and the findings of a bronchial occlusion on bronchoscopic examination, the clinical diagnosis now was changed to that of a carcinoma of the lung. This diagnosis was entertained in spite of the tissue report obtained from the mass occluding the bronchus, which

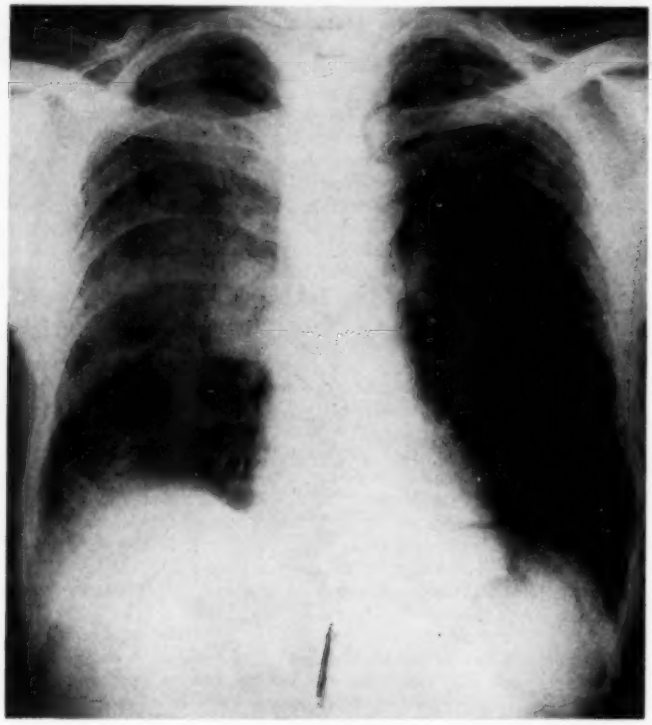

FIG. 6. *Case 11*, J. N. Chest film showing density in right mid lung field.

showed chronic inflammatory changes only. The patient was sent to us in poor general condition for "further care."

He was admitted to Montefiore Hospital in April, 1947. Four more months (a total of eight) elapsed before the final diagnosis was established and surgery was instituted. During this period numerous chest films were taken (figure 6), bronchograms studied, and sputa were examined by means of smears, cultures, and guinea pig inoculations. Three more attempts (a total of five) were made to visualize the lesion with the bronchoscope and to obtain a diagnostic specimen through it. On one occasion, "thin, acrid pus was seen discharging profusely from the right bron-

chus"; on another, the absence of bronchial occlusion, previously seen, was noted. On the last attempt, acute and chronic inflammatory changes were seen. During this entire phase of observation and investigation the patient continued his downward course. Roentgen-rays now revealed an abscess formation within the apex of the right middle lobe and atelectasis of the right lower lobe. The temperature remained within normal limits; the white count rose to 21,000, with 75 per cent polynuclear

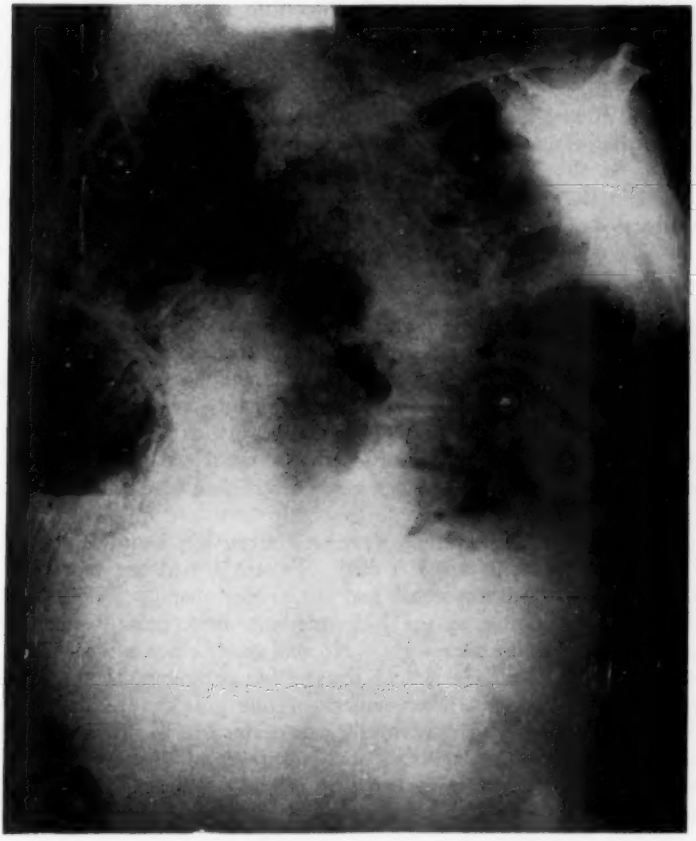

FIG. 7. *Case 11*, J. N., showing fluid level after aspiration of pus.

cells. A needle introduced under fluoroscopic control into the diseased areas yielded 10 c.c. of pus (figure 7). This aspirated material contained no tubercle bacilli or pyogenic organisms; tumor cells were not seen. Thoracotomy followed aspiration. An encapsulated empyema was found and drained. The postoperative course was stormy but the patient recovered. When last seen he was in good general condition. The physical and roentgen-ray findings of the lung were essentially negative.

A nonresolving "pneumonia" in a 63 year old male should be suspected to represent a secondary infection superimposed upon a lung cancer. As is so well known, pneumonia infiltrations with suppuration and abscess formation are frequent complications of lung tumors. It is also generally recognized that lung tumors are frequently beyond the reach of the bronchoscope. Even when a tumor mass is seen, a diagnostic specimen is not always obtainable for histologic examination. Therefore, early aspiration or surgical exploration of chest masses is advocated whenever other methods fail to reveal the nature of the pathologic condition. Aspiration and thoracotomy are essential diagnostic procedures which should be used early in the course of the disease if operable lung cancer is to be disclosed. Their early use in the diagnosis and management of nonmalignant suppurative lung processes is equally important. Rapid and progressive cachexia is an unreliable aid in the diagnosis of lung malignancies, as it occurs in nonmalignant diseases of the lung with great frequency.

Discussion

As can be seen from table 1 and the summaries of these case histories, none of the 11 patients suffered from malignant disease. In the first three, the organ suspected to be the primary site of malignancy was unaffected; in the other eight it was the site of nonmalignant disease. Six of these patients (Cases 3, 4, 5, 7, 9, and 11) are alive: patient 3 is maintained in good condition; patient 4 has returned to his usual occupation; patient 9 is in excellent health; patient 11 has made a complete recovery and is now employable. We have been unable to obtain complete follow-up records on Cases 5 and 7. These people were well when last heard from. Five patients (Cases 1, 2, 6, 8, and 10) died. Patient 1 died one year after an erroneous diagnosis was corrected and the proper therapy was instituted. Her death is attributable to the long-standing unrecognized spinal cord compression resulting in paraplegia. No malignant disease was found on autopsy. Patients 2, 6, and 8 had irreversible pathology at the time of admission. In patient 10, improvement of one year's duration was accomplished by surgery which previously was deemed to be unfeasible. The true nature of this patient's illness was not revealed, however, until her sudden demise, caused by terminal rupture of the appendix. The pathology was not recognized on either previous surgical exploration.

In three of these cases (1, 2, and 4), no biopsy specimens had been taken; in three others (6, 9, and 10), the biopsies were taken but the histologic interpretation was erroneous. Five patients (1, 4, 8, 9, and 10) were explored and misjudged at operation, an inflammatory mass having been mistaken for malignancy. In two patients (3 and 5), exploration would possibly have helped to arrive at the correct diagnosis. In four instances (3, 7, 9, and 11), the roentgen-ray interpretation was misleading; in three

others (1, 5, and 11), pertinent diagnostic aids were not used. The time lapse between the original and the corrected diagnosis ranged from a few weeks to more than six years. In three of these patients (1, 9, and 10), the long duration of the alleged malignant disease, without the deterioration usually expected, raised the initial doubt as to the accuracy of the original diagnosis.

(To be continued)

THE INDUSTRIAL ASPECTS OF CARDIAC INFARCTION *

By G. F. Strong, M.D., F.A.C.P., F.R.C.P. (C), *Vancouver, B. C., Canada*

There has been a change in our concepts of the industrial aspects of cardiac infarction which finds a parallel in the development of the clinical concepts of that condition. The industrial aspects of infarction have shown the same tendency to the swing of the pendulum so frequently encountered in medical thinking in other fields.

Following Herrick's first paper [1] in 1912 on the clinical features of sudden obstruction of the coronary arteries there was little general interest taken in this subject. After the next two papers [2, 3] he published in 1918 and 1919 the condition received a great deal of attention and soon the diagnosis became commonplace. Twenty years later Herrick [4] himself pointed out the danger of over-diagnosis. The industrial aspects of cardiac infarction became apparent much later than the clinical recognition and have been the subject of many articles in current medical literature in the last 15 years. Here too there is danger of the pendulum swinging too far.

This change in our concepts of the compensability of cardiac infarction can be illustrated by the following two cases:

Case 1. In September 1941 a previously healthy 47 year old Provincial policeman in the course of his duty ran a distance of over two and one-half miles in pursuit of a burglar, then drove a car at a rapid speed and under considerable tension for about five miles when he collapsed. He had severe substernal pain extending to shoulders and down both arms. He was taken to hospital where he was treated for myocardial infarction which was later proved by cardiogram. He was awarded compensation and later transferred to Vancouver where he was followed until he died of a second myocardial infarction in July 1945. Autopsy showed old infarction, widespread coronary sclerosis and a terminal fresh infarction.

Here was a clear cut case in which unusual and prolonged effort resulted in myocardial infarction, probably as a result of coronary insufficiency.

Case 2. In November 1947 a 53 year old railway freight conductor on duty near midnight was seen to signal the engineer to start the train stopped on siding, and step onto the first step of the rear platform of the caboose. Within a minute or two he was discovered lying on the ground beside the track as the train slowly moved ahead. The trainman ran back to him, recognized that he was seriously ill and signalled the engineer to stop the train. When help arrived the conductor was dead. Autopsy revealed an extensive coronary sclerosis, coronary occlusion, and recent (microscopic) extensive infarction.

This claim was accepted by the Workmen's Compensation Board and the widow awarded a pension, yet there is no evidence of strain or accident to be found in the case.

* Presented before the Thirty-First Annual Session of the American College of Physicians, Boston, April 17, 1950.

In the instance of the policeman there was ample evidence on which to justify compensation, but in the latter case the only claim that could be put forward was that the coronary accident developed during the workman's working hours. This finding led to a study of the whole question of compensability of claims for cardiac infarction and for this purpose a series of 20 cases awarded compensation in British Columbia, including the two mentioned above, were studied. Of these, four including the second already referred to, were submitted to the Chief Medical Officers of the other Canadian Compensation Boards in order to determine the action that would have been taken in other Provinces.

This discussion is not presented by way of criticism of the action of the British Columbia Workmen's Compensation Board, but rather to bring to the attention of the medical profession, and particularly the members of this College, that there is wide variation in the views expressed by specialists in cardiology regarding the relation between physical effort and strain and myocardial infarction. The Compensation Boards are naturally influenced by one or another of these different views.

TABLE I

Cardiac Infarction

In industrial workers may occur as result of:
1. Penetrating or non-penetrating wounds of the chest.
2. Secondary shock following accidents, or operations necessitated by accidents, burns, asphyxia, etc.
3. Extra physical strain ?
   ? Accident or incident.
4. Coronary occlusion developing during hours of work.

Table 1 presents the instances of cardiac infarction that may occur in industrial workers. (1) Infarction may be due to penetrating or non-penetrating wounds of the chest. Of these the former are rare but the latter, and especially the "steering wheel injury" in which the anterior chest wall is subject to violent trauma, is all too common. Bruising of the myocardium and actual injury to the coronary arteries may occur. (2) Infarctions occurring during shock following accidents, or the operations necessitated by accidents, or after burns, or asphyxia, are well recognized and offer little ground for difference of opinion. (3) Infarctions occurring after extra physical effort, or a minor accident or incident, with resulting physical strain, offer much room for discussion. In the first place it must be decided what constitutes *extra* or unusual strain. This will vary in different occupations and between two workmen. The ordinary activity of a stevedore would constitute unusual strain for a carpenter, and as between two stevedores, one might be capable of much greater "bursts of effort" than another. It is in this category that the greatest argument occurs. Time relationship is also important. Where the symptoms of myocardial infarction develop at the time or immediately after the strain the causal relation would seem

certain, but where the symptoms develop many hours later cause and effect might be questioned. When it comes to deciding just how long an interval might be accepted there is real difficulty. A few hours, two, four or six, might seem acceptable; over 12 hours, and certainly over 24 hours would raise many questions, and yet it is well known that *infarction may start some time prior to the onset of symptoms.* (4) Claims arising in instances in which cardiac infarction has occurred during working hours without any antecedent factors should hardly warrant the serious consideration of our Compensation Boards. If such claims are to be accepted then any degenerative disorder, the first symptoms of which happen to occur during working hours, would be compensable. This is obviously not the intent of Workmen's Compensation legislation and it is in addition grossly unfair to other workmen who through chance happen to develop their first symptoms during other than working hours.

Prior to 1940 there were few claims granted in British Columbia for cardiac infarction resulting from effort (Class 3, table 1) but since that time such claims have been approved with increasing frequency. Examples will be cited later to show that claims for disability and death have been approved in instances where only slight and not necessarily extra or unusual physical strain preceded the development of cardiac symptoms.

While such cases may admit of some ground for argument there would appear little reason to accept as compensable claims arising solely because the coronary accident occurred during working hours (Case 2 above: Class 4 in table 1). If such evidences of degenerative cardiovascular disease are to be accepted as compensable merely because the dramatic incident of myocardial infarction happens to occur during working hours, then there would seem to be no limit to the compensability of industrial workers on purely medical grounds.

In this discussion it is admitted that cardiac infarction never develops except on the basis of coronary sclerosis. It is granted that no amount of effort or physical strain can harm the normal heart.[5] Coronary sclerosis is a common condition occurring at any age, more frequent in men, and of course, more common in older age groups. With the increasing span of life in the population in general there is some increase in the average age of industrial workers. This may be more true in British Columbia than elsewhere on this continent because of the fact that the whole province and particularly the industry in the province is comparatively young. The province has become a haven for older age groups on account of the equable climate. Also many have come here to retire but for various economic reasons have been forced to become earners again. In one large industry the percentage of workers over 50 years of age in 1925 was 11.5 per cent and in 1950 this same group made up 23 per cent of the employees. Industry is therefore vitally interested in the increasing incidence of coronary disease and in the tendency to award compensation to a greater percentage of these cases.

Coronary sclerosis is insidious and may run a varied course. Many victims of this condition develop congestive heart failure and are forced to give up their work because of the symptoms of that condition. Of the cases of coronary sclerosis that develop the anginal syndrome many will develop infarction or congestive failure at a time entirely unrelated to their occupation.

It is in relation to the effect of effort on the production of infarction that there is most argument.[6, 7] In those that develop infarction on a basis of coronary occlusion due to thrombosis, or the arteriosclerotic process itself, there would seem little evidence in favor of effort or strain as a precipitating factor. Master [8] has shown that in a large series of cases of infarction of this sort preceding activity has no causal relation. The majority occur when the patient is asleep, at rest or engaged in mild activity. The question of whether physical strain can rupture an atheromatous plaque or cause the intimal hemorrhages shown by Winternitz [9] to be a part of the arteriosclerotic process is debatable. According to Master these hemorrhages are as frequent in patients with low blood pressure or who have been confined to bed as in any others. Whether painful experiences, vigorous effort, or periods of alarm can alter clotting time and so play a part in the production of intra-arterial thrombosis is at present under study.[10] On the other hand where the infarction occurs as a result of coronary insufficiency as in Case 1 there would seem ample reason to regard the effort as a causal factor.[11] When a distinction is attempted between ordinary and unusual exertion there is real difficulty. When effort produces infarction it is obviously relatively excessive for that individual at that time. Strenuous effort continued for some time (as in Case 1) by an individual with sclerotic coronary arteries may produce infarction as a result of coronary insufficiency—"infarction without occlusion." Boas [12] claims that the distinction between infarction due to coronary occlusion and that due to coronary insufficiency is an academic one, yet in the former effort plays little if any part, whereas in the latter exertion or physical strain may be the causal factor.

The following cases of cardiac infarction in industrial workers in British Columbia were selected as examples resulting from minor accident or physical strain. In most of these definite extra and unusual effort can be shown but in a few the effort would seem to be well within the usual limit for the occupation.

Case 3. Refrigerator car inspector, aged 55. On night duty. At 4.45 a.m. one winter night experienced considerable strain in lifting a partly frozen hatch cover weighing 80 lbs. He felt pain in chest and left arm but continued his work until 8.00 a.m. when he took the street car home and on the car developed substernal pain. He transferred once, walked one block to his home and collapsed at the door. A doctor was called who diagnosed cardiac infarction which was confirmed by cardiogram.

Here there is some question as to the actual physical strain. This man was carrying on his usual work and had undoubtedly lifted heavy hatch covers many times before. On this occasion the hatch cover was partly

frozen and this may have added an unusual element to the strain. His actual substernal pain developed about two and one-half hours after the strain.

Case 4. Engine fitter, aged 62, had been off work for nearly one year recovering from a previous myocardial infarction, when seven months after resuming his usual occupation at 2.40 p.m. he was drilling a sea valve under the floor plates of a ship. He was working in a cramped position and exerting considerable effort when he collapsed. A doctor was called who diagnosed cardiac infarction and sent him by ambulance to hospital. The patient died at 6.40 p.m. Autopsy showed old and recent myocardial infarction.

Here a workman with previous infarction was engaged in his usual occupation that involved considerable physical strain. He collapsed with symptoms and signs of another, terminal cardiac infarction.

Case 5. Surveyor, aged 45. Immediately after breakfast he climbed 400 feet up a steep mountainside to the tunnel of an old mine. He walked 150 feet along the tunnel, collapsed and died. Autopsy revealed coronary occlusion with microscopic myocardial infarction.

The effort here was unusual but not more than this man and others in his party had sustained on many occasions.

Of the preceding cases brief abstracts of four, numbers 2, 3, 4 and 5, were submitted to the Chief Medical Officers of seven other Provincial Workmen's Compensation Boards in Canada. These medical officers were asked to consider these claims and indicate what action would probably have been taken by their respective boards. Since only brief abstracts were submitted and the other medical officers were not in possession of all information available to the British Columbia Board too much significance cannot be attached to these replies. One of the medical officers replied in general terms only, the others indicated that the claims would have been *allowed, disallowed* or, if the information submitted was regarded as insufficient, would have been considered. These replies are set out in table 2.

TABLE II

Summary of Replies from Other Provincial Compensation Boards in Canada Regarding Four Cases Granted Compensation in British Columbia

Serial No.	Age, Occupation	Category Table 1	1	2	3	4	5	6	7
2	53, Freight car conductor	4	Disallowed	Disallowed	Disallowed	Disallowed	Disallowed	Disallowed	Answered only in general terms
3	55, Freight car inspector	3	Allowed no T.D.	Considered no T.D.	Disallowed	Considered, allowed if strain unusual	Disallowed	Allowed	
4	62, Engine fitter	3	Disallowed	Allowed	Disallowed	Questioned, probably allowed	Allowed	Allowed	
5	45, Surveyor	3	Probably disallowed	No reply	Disallowed	Allowed	Disallowed	Considered on merits	

It is obvious that the replies indicate a considerable variation in opinion. In Case 2 all other boards would have disallowed the claim, but in other cases there was not this agreement. One board (column numbered 3) would have disallowed all four claims submitted. It is not unlikely that the same variation might be found among different compensation boards in the States.

The difference of opinion shown in these replies is a reflection of the great variation of thought in this regard to be found in current medical literature. It is possible to defend two quite opposite points of view by quoting opinion of recognized authority.[6, 7] It is time the medical profession made some

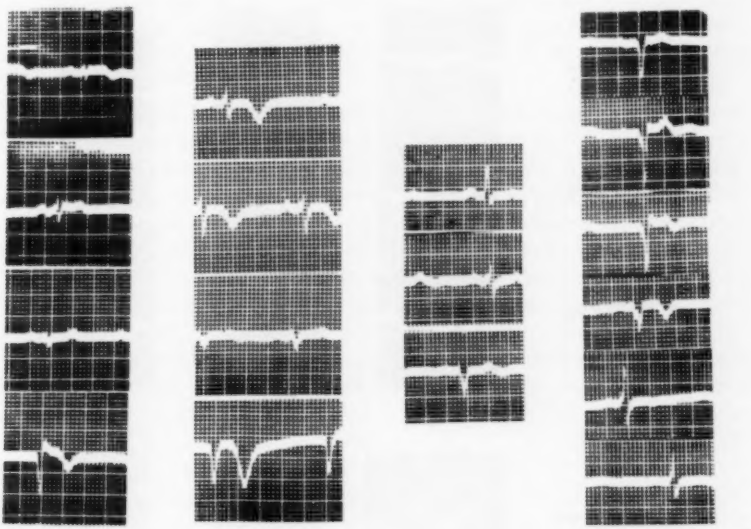

FIG. 1. Electrocardiograms, Case 12. June 19, 1947, limb leads—Lead IV F. July 14, 1947, limb leads—Lead IV F. June 15, 1948, on left limb leads, on right V_{1-6}.

attempt to set its house in order and, though unanimity would be out of the question, there should be some agreement on general principles.

Of the 20 cases from the files of the British Columbia Workmen's Compensation Board which were examined, three others are worth particular comment.

Case 12. Diesel engineer, aged 43. On June 9 after strenuous lift developed a "heavy feeling" in his chest. Carried on his work and on June 15 was conscious of pain in epigastrium, attributed to indigestion. On June 18, nine days after first pain, he carried a 125 lb. tool box 100 yds. He collapsed with chest pain. He was flown to a doctor who that night diagnosed infarction, confirmed by serial cardiograms. He continued to have symptoms of angina and congestive failure. Total and permanent disability was allowed.

Here there were prodromal symptoms with infarction after some extra but not actually unusual exertion. This young man showed typical cardiograms illustrated in figure 1.

Case 17. Truck driver, aged 50, while loading crated machinery on a truck tried to move a heavy case alone, felt distress in chest and dyspnea and had to rest for a half hour. He drove the truck to the garage and went home on the street car. He enjoyed his supper and was well all evening and slept well. He had a good breakfast. On way to the street car there was recurrence of more severe chest pain. He went to a doctor instead of to work and was sent to hospital. Cardiogram three or four hours after morning pain showed depressed R–T segments in Leads II and III, in-

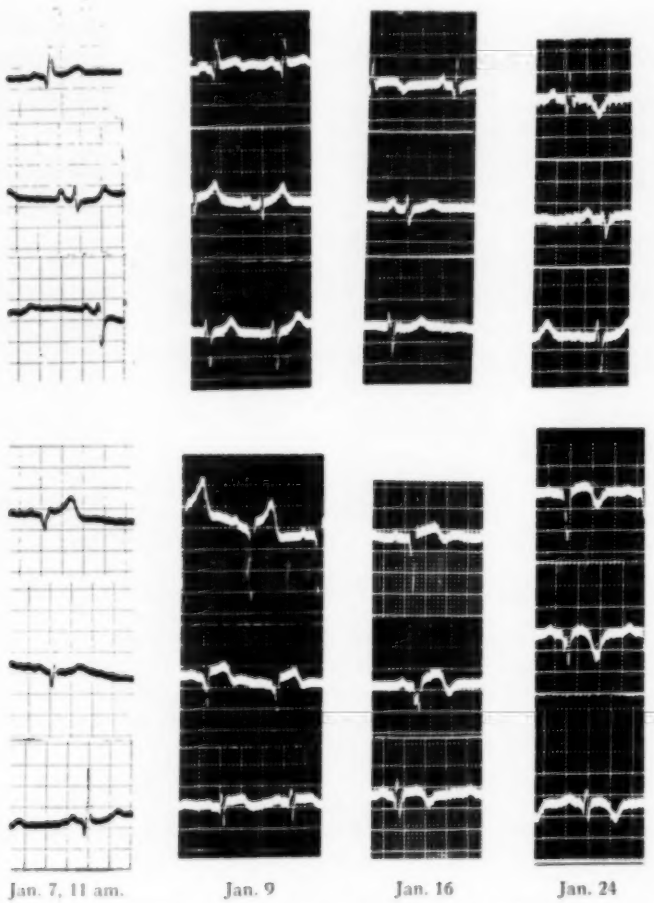

FIG. 2. Electrocardiograms, Case 17. Top, limb leads. Below, V_2, V_4, V_6.

dicating coronary insufficiency. He was well for 30 hours, then developed severe pain. Cardiogram 48 hours after first tracing showed typical anterior infarction with $T_{1 \text{ and } 4}$ inversion, figure 2.

The question here is, did chest pain that followed effort on first afternoon indicate the onset of infarction, or did he have coronary insufficiency for first and second day, and then develop infarction? Was the whole attack attributable to the effort, or was relation coincidental?

Case 20. Carpenter, aged 44, employed by same company for 19 years, for last three years given light work because of angina pectoris. He suffered a superficial flash burn of face at 2.00 p.m. A doctor dressed the burns and gave him morphine gr. ¼. He was sent home to bed. At 7.00 p.m. he had severe chest pain and vomiting. The doctor was called—pulse 80, regular, blood pressure 145/90—more morphine given—continued pain—death 9.30 p.m. Autopsy showed a fresh thrombus in sclerotic right coronary artery.

Here a normotensive man with effort angina was kept on as an employee on light work. He suffered a minor accident and because of his preëxisting coronary sclerosis developed a fatal coronary occlusion seven to eight hours later. This is probably an example of category 2, table 1. This man illustrates the danger to industry in keeping on the pay-roll under the present interpretation of compensation in British Columbia an individual with known coronary sclerosis. This man was a poor industrial risk. A man with a normal heart would not have died as a result of the minor accident this man experienced.

Of these 20 cases most of which occurred in the last three years, eight have died, and of the 12 surviving nine have some continuing disability, two have returned to work, and one is still convalescing. The fact that of the 12 surviving patients all but three have some residual disability must be attributed in part at least to the attitude of the medical profession. There is still too much pessimism regarding the prognosis of cardiac infarction. These industrial cases are unfortunately often given the wrong impression from the onset of their illness. They are imbued with the idea that their heart condition developed as a result of exertion and that any future activity will be harmful. This, coupled with the comfort of a permanent disability allowance, means that complete recovery is nearly unknown in this group.

The medical profession and particularly the members of this College should urge a different approach to these patients. The first medical attendant should instill the idea that they will recover and that ordinary activity will not bring on a recurrence of their cardiac disorder. We should also be more critical in our analysis of the causal relationship between effort and cardiac infarction in every instance. In the main the compensation boards will be influenced by the attitude of the internists in this regard.

In this connection it is important to keep clear the distinction between awards of compensation for industrial accidents or occupational hazards and pensions to war service personnel. In the latter case the State assumes

full responsibility for anything that happens, but industry under industrial commission or compensation board regulations should be concerned only with accidents or occupational hazards.

Rehabilitation is one of the most important trends of the last decade. Rehabilitation of individuals with coronary sclerosis that developed cardiac infarction while on the job should start with the doctor that sees the patient first. In those that recover, the number returned to duty should be much greater than at present. Industry must be prepared to accept these individuals in jobs suited to their cardiac capabilities. In order to do this preemployment examinations become essential. An employer should know the physical condition of the workman he is employing. In addition to the preëmployment examination, and particularly for employees over 50, annual health examinations are of proved value, and in this age group the examinations should include an electrocardiogram and chest x-ray. With this information available workmen can be categorized and the individuals with significant coronary artery involvement put in jobs where they will not be subject to extra strain, and where trivial accidents should occur less frequently. Under these circumstances industry should not be penalized if one of these cases succumbs to a cardiac infarction following a minor accident or strain insufficient to cause death in a healthy individual. The principle of the "second accident" should be accepted in these cases. For example, if a workman loses an eye and later takes a job with a second employer during the course of which an accident results in the loss of his remaining eye, the second employer is not assessed on the basis of causing total blindness. In the same way, if an employer employs a workman with a known incipient cardiac disability like coronary sclerosis, he should not be assessed the full amount for death or disability of that individual following trivial accident or physical strain.

Summary

Few will question the compensability of cardiac infarction occurring as result of categories 1 and 2 in table 1. In category 3 there will be much less agreement and each case must be decided on its merits. If compensation is to be limited to the result of accident then many claims arising under this category should be disallowed. If, on the other hand, compensation should be extended to cover industrial hazards, and unusual strain can be shown, such claims may be accepted. Time relationship is important and coincidental coronary accidents must be kept in mind. Physical strain or unusual effort is more likely a cause in those instances where coronary insufficiency can be shown to be the precipitating factor of the infarction. The cardiac symptoms should appear at the time of the effort and be more or less continuous until the diagnosis of infarction is established. Claims arising under category 4 should be disallowed, as purely coincidental and not in any way compensable.

Conclusion

1. Twenty instances of cardiac infarction allowed compensation in British Columbia have been reviewed. There were examples of infarction resulting from minor accidents, extra physical strain, or occurring during working hours.

2. Four of these claims were submitted to the Chief Medical Officers of the other Provincial Workmen's Compensation Boards in Canada.

3. There is notable lack of agreement on the compensability of such claims.

4. The medical profession should attempt to establish more definite general principles regarding the relation between effort or physical strain and the production of cardiac infarction.

Grateful acknowledgment is made of the assistance given by Dr. Giles B. Murphy, Chief Medical Officer, British Columbia Workmen's Compensation Board, who not only made available the cases for this review but secured the views of the other Provincial Compensation Boards.

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CASE REPORTS

THE CRITERIA FOR CLINICAL DIAGNOSIS OF SYPHILIS OF THE LUNG; WITH REPORT OF A CASE*

By Byron F. Royce, M.D., *Hayward, California*

In 1924, Howard [2] stated that 200 cases of syphilis of the lung had been reported in the literature. He felt that this disease could no longer be considered a rarity. The majority of cases reported were from large autopsy series. These reports are reviewed in papers by Hartung and Freedman [4]; Jacobs [5]; Hamilton and Wexler [10]; Lyons, Brogan and Sawyer [15]; Wilson,[21] and Kulchar and Windholz.[22] Denman [5] and Warring [13] stated that syphilis of the lung cannot be definitely diagnosed clinically. These authors considered clinical pulmonary syphilis a rare condition, as did Reynolds and Moore.[12] However, cases without autopsy or demonstration of the *Spirochaeta pallida* have continued to appear in the literature.

The criteria for the clinical diagnosis of syphilis of the lung have been presented by Hartung and Freedman,[4] and Pearson and De Navasquez.[11] These criteria have varied little with different authors except in their application. They are summarized as follows:

1. History of syphilis. Failure to obtain a history of infection should not rule out the possibility that a pulmonary lesion may be luetic in origin.[22]

2. Signs and symptoms of pulmonary disease. The signs are usually marked, and the symptoms are frequently mild. There is often an anomalous history of pulmonary disease. Hemoptysis, productive cough, loss of weight, and fever may be present.

3. Exclusion of other forms of pulmonary disease. Most authors consider absence of tubercle bacilli in the sputum sufficient to rule out tuberculosis. However, more painstaking efforts should be made to obtain evidence of pulmonary tuberculosis. Other specific tests are done as indicated.

4. Positive serologic test for syphilis. This is not an absolute requirement. Pulmonary syphilis has been reported in sero-negative individuals.[23]

5. Demonstration of the Spirochaeta pallida. The spirochete of syphilis can rarely be demonstrated in pulmonary syphilis, as in other tertiary lesions.

6. Radiographic evidence of pulmonary disease. There are no definitive roentgenologic characteristics. The most common manifestations were summarized by Pearson and De Navasquez as follows: "(a) Infiltration, lobar or patchy in distribution, and involving one or more lobes. (b) Opacities, oval in shape, single or multiple, most often in the lower lobes, often not connected with the hilum, and measuring in diameter from a few millimeters to several centimeters. (c) Generalized accentuation of the bronchial and vascular shadows, extending from the hilar regions to the periphery. (d) Opacity of one lobe, or a whole of one side of the chest with displacement of the mediastinum towards the side of the lesion, denoting fibrosis or atelectasis which may be accompanied by pleural effusion."

* Received for publication March 18, 1948.

7. Therapeutic test. Olsan and Chambers [6] reported a case of syphilitic pneumonia treated successfully with arsenicals. However, arsenicals have been considered by most authors too nonspecific in their effects to be dependable as a therapeutic test.[17] Mercury or bismuth was recommended before the advent of penicillin. Wilson [21] stated that iodides were too non-specific for use in a therapeutic test, but recommended a trial of penicillin. The non-specific effects of arsenicals and penicillin were recognized by O'Leary and Ockuly.[18] They pointed out, however, that the response of non-syphilitic pulmonary disease to these agents is more likely to be of short duration and to be followed by recurrence. Kulchar and Windholz [22] stated that it is exceptional for nonsyphilitic disease of the lung to respond with the thoroughness and rapidity of syphilis to anti-luetic therapy. General clinical improvement usually follows anti-syphilitic treatment, although the roentgenologic response is considered of greatest importance. Change in serology does not necessarily follow adequate treatment.

8. Presence of associated syphilitic lesions in other organs.

The following case is believed to satisfy the present-day criteria for a clinical diagnosis of syphilis of the lung.

Case Report

A 22 year old single white female was admitted October 16, 1946. She complained of weakness for six months. Persistent nonproductive cough and dyspnea on exertion were noted for one month prior to admission. She had lived on a farm in Texas all her life until a month before hospital entry. The only previous illnesses were measles, chickenpox and mumps during childhood. There was no history of symptoms or signs of syphilitic infection.

In 1941, at the age of 16, she developed a tender swelling in the right epitrochlear area. This slowly subsided without treatment. During the next two years she noted similar tender enlargements in the right and left axillae, and both sides of the neck. These also subsided spontaneously. In 1945, the left elbow became swollen, warm and tender. In addition, tender swellings appeared in the left axilla. These swellings subsided in "a few weeks" except for one in the left cervical area. Later in 1945, swelling and tenderness of the left knee developed. No concomitant inguinal enlargement was noted. Spontaneous subsidence again occurred.

Physical examination on admission to this hospital revealed a thin, pale white female. The temperature was 100.6° F. The pulse was regular at 104 per minute. The blood pressure was 100 mm. systolic, and 65 mm. diastolic. The weight was 85 lbs. (38.6 kg.). The oral and nasal mucous membranes were pale. There was a firm, mobile, slightly tender lymph node in the left muscular triangle of the neck. This was approximately 2 cm. in its greatest diameter. The left hemithorax appeared slightly smaller than the right. There was dullness posteriorly over the left apex. Bronchovesicular breath tones and fine moist râles were heard anteriorly and posteriorly in the left upper chest. There was slight left dorsal scoliosis, and an increase in dorsal kyphosis was noted at the level of the twelfth dorsal vertebra. Considerable tenderness was elicited bilaterally in the paravertebral areas at the lower dorsal level.

Laboratory examination revealed a hemoglobin of 9.5 gm. (56 per cent); the leukocytes were 5,750 per cu. mm.; segmented neutrophiles, 64 per cent; nonsegmented neutrophiles, 17 per cent; lymphocytes, 17 per cent; eosinophiles, 1 per cent; basophiles, 1 per cent. Urinalysis showed no significant abnormality. The Kline test was positive. Quantitative Kolmer tests on four occasions showed complete fixation of complement in the first five tubes. The serum proteins were 6.92 gm. per 100 c.c.; serum albumin 3.76 gm. per 100 c.c.; and globulin plus fibrin

3.16 gm. per 100 c.c. The sedimentation rate was 96 mm. per hour (Westergren). Agglutination for *Brucella abortus* was negative. Tuberculin (O.T.) skin test 0.01 mg. (1:10,000 dilution) was negative on three occasions, as was 0.1 mg. (1:1000 dilution) and 1.0 mg. (1:100 dilution). Coccidioidin skin test in a dilution of 1:1000 was negative. One sputum examination (24-hour concentration) after the use of expectorants revealed no acid-fast organisms. There was insufficient sputum for further adequate specimens. Smears and guinea pig inoculation of gastric contents on two occasions revealed no evidence of tuberculosis. The spinal fluid contained no

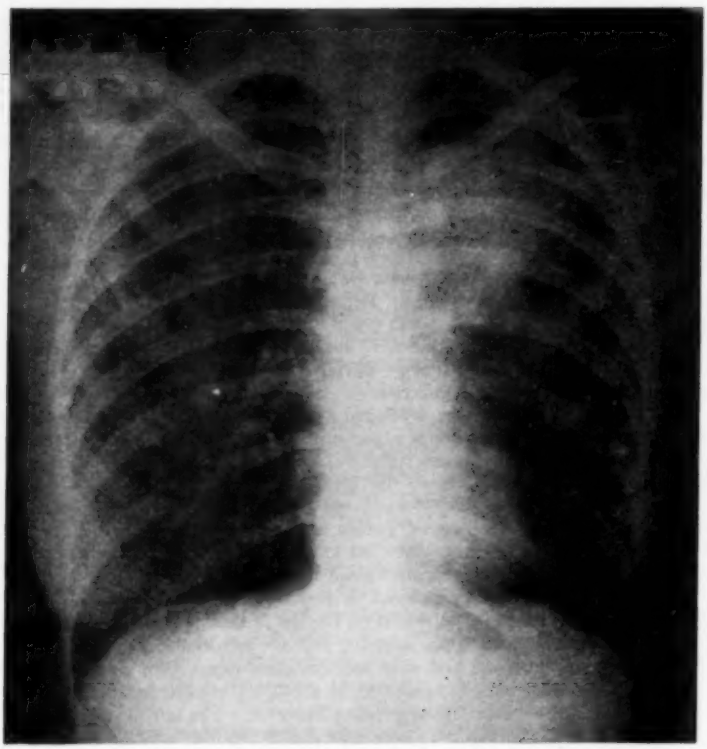

FIG. 1. Roentgenogram of chest taken October 16, 1946, showing hazy infiltration extending into the left upper lung field.

cells. The spinal fluid Wassermann and colloidal gold tests showed no abnormality. Removal and section of the enlarged node in the left supraclavicular area revealed "slight chronic lymphadenitis." Two c.c. of bloody fluid were aspirated from the area of the twelfth dorsal vertebra on November 29, 1946. No acid-fast organisms were found on direct smear, and cultures for tuberculosis were negative after eight weeks. Forty c.c. of slightly cloudy yellow fluid were aspirated from the right knee on December 10, 1946. This contained 2,080 leukocytes, 60 per cent of which were neutrophiles, 30 per cent lymphocytes, and 10 per cent monocytes. Direct smear, aerobic and anaerobic cultures were negative.

Roentgenograms of the chest showed a circumscribed area of density, more opaque centrally, located in the left upper lung field. Fluoroscopy revealed this area to be continuous with what appeared to be enlarged posterior mediastinal lymph nodes. Roentgenograms of the spine showed a sclerotic destructive process involving the twelfth dorsal vertebra, with only the lower one-third of the vertebral body remaining intact. Bronchoscopy revealed inflammation of the mucosa of the left main stem bronchus, with 33 per cent stenosis. A bronchial biopsy was interpreted as active caseating tuberculosis. Two subsequent biopsies revealed normal bronchial mucosa.

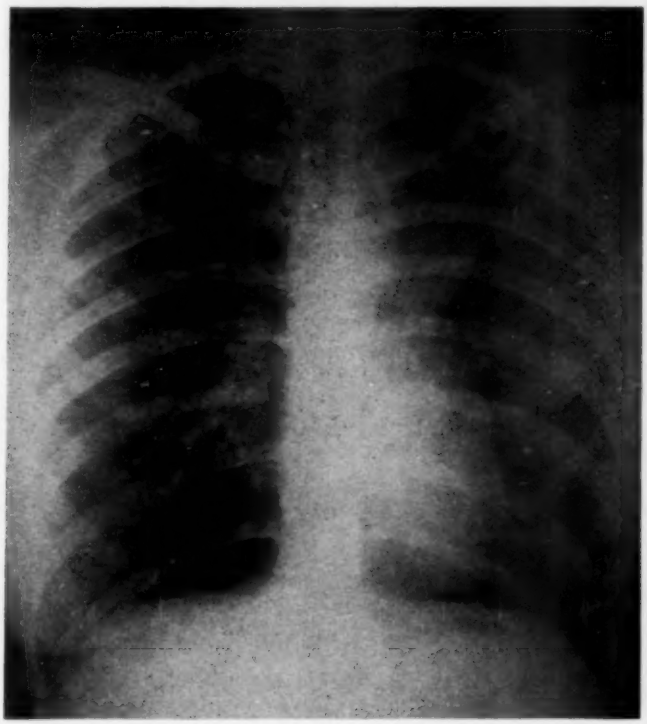

FIG. 2. Roentgenogram of chest taken in February 1947 after the patient had received 7,960,000 units of penicillin. The thin fibrotic strands extending into the left upper lung field have persisted with little change to the present time (December 1947).

Biopsy material injected into guinea pigs on two occasions revealed no evidence of tuberculosis.

The patient was given supportive treatment, including a high caloric diet and ferrous sulfate. She was placed on strict rest on a Bradford frame. On November 24, 1946, penicillin was started intramuscularly every three hours. This was continued until January 12, 1947, for a total of 7,960,000 units. She was also given bismuth subsalicylate 0.2 gm. intramuscularly twice weekly for a total of 1.8 gm. During this time, fever which had been ranging between 99.4 and 100.8° F. dropped

to normal. The hemoglobin rose to 11.2 gm. (66 per cent). The sedimentation rate dropped to 17 mm. per hour on January 3, 1947. Roentgenograms showed decrease in the size of the homogeneous density in the left upper chest. Mapharsen 0.06 gm. intravenously was given in five weekly doses, beginning March 6, 1947. Bronchoscopy on May 16, 1947, showed reddening and 20 per cent stenosis of the left main stem bronchus, although the instrument could be passed through this area. Roentgenograms of the spine on May 22, 1947, revealed increased calcification of the

FIG. 3. Roentgenogram of spine showing lateral view of destructive process involving the twelfth dorsal vertebra (February 1946).

twelfth dorsal vertebra. At this time, the lesion was considered to be stable and bed exercises were begun. An Arnold back brace was fitted, and she began ambulation on June 20, 1947. A month later, the weight was recorded as 109 lbs. (49.54 kg.). On July 18, 1947, the Kline test was positive, and the quantitative Kolmer examination showed complete fixation of complement in the first five tubes. These tests were repeated in October, 1947, with identical results. Also in October, 1947, histoplasmin skin test* (1:1000) was negative.

The patient has continued clinic visits, and she receives 0.2 gm. bismuth subsalicylate intramuscularly weekly. At present (December, 1947), she is entirely free of symptoms and is allowed full activity. The roentgenogram shows only fine fibrotic strands radiating into the left upper lobe in the left chest.

Because of the possibility of congenital origin of the disease, the available members of the family were tested. The father, two brothers, and one sister had negative Kahn tests. The patient is the third of six children. The two youngest children were not available for testing. There is no history of syphilis or antiluetic therapy in other members of the family. The patient's mother died in 1931 of diphtheria. This occurred during a local epidemic. All members of the family except the youngest child, and the patient had diphtheria at that time.

Discussion

History of primary or secondary manifestations of lues could not be elicited in this case. The absence of stigmata and negative serologic tests in the patient's family are against congenital syphilis. All authors agree that clinically significant pulmonary involvement is a manifestation of the tertiary stage of syphilis. This excludes, of course, the pneumonia alba of infancy, and mild respiratory tract involvement during the secondary stage. The age of onset in this instance was earlier than any cases found in the available literature. Hartung and Freedman reported one case in a 25 year old male. Several other instances in the third and fourth decades have been reported.

The lesion involving the twelfth dorsal vertebra is thought to be syphilitic in origin. Certainly, great caution should be exercised in the interpretation of this as well as of the pulmonary disease. However, the evidence appears to favor causation by syphilis. Repeated examinations were made for the possibility of tuberculosis. The bronchial biopsy specimen regarded as tuberculous tissue is probably inconclusive in view of the other evidence. It is sometimes very difficult to differentiate between gumma and tubercle, both histologically and grossly.[3, 8, 16] A persistent high titer of serologic tests for syphilis is strongly against the possibility of biological false positive reaction.[20]

Bronchial stenosis on the side of the lesion was demonstrable in this case. It appears that the possible rôle of bronchial obstruction has not been sufficiently stressed in the literature. Denman stated that atelectasis may occur due to stricture by scar or pressure by gumma causing bronchial obstruction. Under these conditions, bronchiectasis with induration and fibrosis may supervene. Jacobs noted that anaerobic conditions suitable for invasion by the spirochetes often prepare the ground for infection. No specific mention was made of bronchial obstruction. Stokes[17] points out that gummata of the trachea or bronchi are rare. The symptoms are inspiratory stridor, dyspnea and paroxysmal attacks of brassy cough. Bronchiectasis may follow this condition. Conversely, Boyd[24] states that gummatous ulceration of a bronchus with subsequent stenosis

* Supplied by Eli Lilly Laboratories.

is the commonest and most clearly defined lesion of pulmonary syphilis. Richards [19] mentions tracheobronchial syphilis with stenosis as one of the causes of bronchiectasis.

Of 31 cases of pulmonary syphilis reported in the literature since 1923,[1] 16 were not bronchoscoped and did not come to autopsy. Therefore, no definite statement can be made as to the presence or absence of bronchial lesions. One case showed no bronchial obstruction on bronchoscopy, but bronchiectasis was found at necropsy. Two cases had bronchial lesions on bronchoscopy, and atelectatic areas at autopsy. Bronchoscopy revealed bronchial inflammation and narrowing in four instances which did not come to postmortem examination. Autopsy reports of seven cases which had not been bronchoscoped previously reveal five instances of bronchial occlusion and atelectasis. There was no mention of atelectasis or description of the bronchi in two autopsy reports. In one case, the bronchial tree was normal in the presence of parenchymal gummata.

It has been previously pointed out [11] that the pathologic picture seen is often the end result of long-standing disease. The gross and microscopic findings depend greatly on the developmental stage at which they are seen. This is particularly true of bronchiectasis and fibrosis. The above considerations suggest frequent bronchial involvement in pulmonary syphilis. Bronchial narrowing may initially be caused by some agent other than syphilis. With this preparation, pulmonary parenchyma may be rendered susceptible to localized syphilitic involvement in a luetic individual. In some instances, gumma of a bronchus may precede secondary pyogenic invasion of the involved bronchial segment. Further clarification of these possibilities should provide a better understanding of the pathogenesis of pulmonary syphilis.

Bronchoscopy appears to be a useful diagnostic adjunct in cases of suspected pulmonary syphilis. Holinger [9] mentions the use of this procedure in the differentiation of pulmonary lesions of obscure etiology. It is of value both in the determination of the presence and the degree of bronchial involvement, and in the recovery of biopsy material for microscopic examination. The most significant specimen of sputum for smear, culture, and guinea pig inoculation is obtained during or after bronchoscopy. Probably much of the skepticism in the past regarding clinical diagnosis of pulmonary syphilis has been due to lack of thoroughness to rule out other causes of pulmonary lesions. Great reliance has been placed on absence of tubercle bacilli in the sputum by most authors. In some instances, sputum was not examined, or tuberculosis was ruled out on a single negative sputum specimen.[14, 22] Bronchoscopy should enhance the value of a negative report in any case.

It appears that syphilis may account for certain otherwise obscure pulmonary lesions. At the present time, clinical diagnosis of syphilis of the lung depends on several well-recognized criteria. These have been summarized above. They will undoubtedly be revised with further observation of the disease. That pulmonary syphilis often goes unrecognized has frequently been stressed. This manifestation of syphilis should be more often identified with further clarification and adherence to the clinical criteria for diagnosis.

Conclusions

1. Clinical diagnosis of syphilis of the lung is permissible with strict adherence to proper criteria for diagnosis.

2. Bronchoscopy is a useful diagnostic adjunct, both in the evaluation of presence and degree of bronchial involvement and in the exclusion of other disease.

3. The rôle of bronchial stenosis in the pathogenesis of pulmonary syphilis should be further clarified.

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RHEUMATIC NEPHRITIS *

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DESCRIPTIONS of rheumatic nephritis appear rarely in the medical literature. Albuminuria, cylindruria, and hematuria have been reported to occur in acute rheumatic fever by Cecil,[1] Michelazzi,[2] Lichtowitz,[3] and Goldring and Wyckoff.[4] These authors, however, have noted no instances of acute glomerulonephritis in rheumatic fever. The rarity of renal involvement in this disease is pointed out by Rolly [5] and Baehr and Schifrin.[6] Cecil [1] is of the opinion that many cases of idiopathic nephritis are but instances of rheumatic kidney disease. We, too, believe that rheumatic nephritis is an entity to be included among the protean manifestations of rheumatic fever.

CASE REPORT

A 25 year old unmarried Negro was admitted to the surgical service of the Army Air Forces Regional Station Hospital, Orlando, Florida, in January, 1945. He complained of sharp, intermittent abdominal pain with nausea of five days' duration.

The past history is significant in that the patient was hospitalized four weeks previously for an acute tonsillitis.

The present illness began with sharp, diffuse, intermittent, periumbilical pain associated with nausea and abdominal distention. Examination revealed extreme tympanites, with absent peristalsis, normal blood pressure, leukocytosis, a precipitate of albumin in urine, microscopic hematuria, elevated erythrocyte sedimentation rate (Westergren method) and nonprotein nitrogen.

The occurrence of granular casts on the second hospital day, together with the persistent albuminuria, hematuria and impaired renal function as revealed by urogram, led to the conclusion that the abdominal pain and distention were secondary to some renal involvement. The patient was then transferred to the medical department on the third hospital day. The significant physical and laboratory findings were as follows: extreme abdominal distention, absent peristalsis, normal blood pressure, normal heart sounds, normal lung fields, pretibial, sacral and facial edema, leukocytosis, and elevated sedimentation rate and nonprotein nitrogen. The plasma proteins were below normal. A persistent albuminuria, cylindruria, gross hematuria and granular casts were present. Attempts to overcome the distention and uremia were futile. During the first six days (see chart), the blood pressure rose from 110 systolic and 70 diastolic to 149 systolic and 90 diastolic, and within the next seven days (see chart) it rose to 170 systolic and 120 diastolic.

During this interim the patient's condition became progressively worse. Penicillin (a total of 960,000 units intramuscularly) was administered to no avail. The sedimentation rate, nonprotein nitrogen, and blood pressure remained elevated. The plasma protein continued to fall, together with the development of a progressive oliguria (see chart). A mitral systolic and an aortic diastolic murmur were clearly audible for the first time on the thirteenth hospital day. An electrocardiogram at this time revealed prolongation of the P–R interval (0.25 second) (see chart).

All attempted methods of therapy failed to alter the progressive seriousness of the patient's condition. It was then decided to try the effect of judiciously administered intravenous sodium salicylate (8 grams in 24 hours), its inherent dangers being fully recognized. The drug was first given on the fifteenth hospital day, and

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within 48 hours a dramatic clinical response occurred. The abdominal distention had markedly decreased, peristalsis returned, edema diminished, and decided subjective comfort ensued. Within 96 hours, the abdominal distention and edema had completely disappeared. The laboratory studies showed a most favorable response (see chart). The blood pressure, temperature, nonprotein nitrogen, and sedimentation rate approached normal levels. There was a marked decrease of the albuminuria and hematuria. Three days after the administration of salicylates was begun (eighteenth hospital day), the patient developed clinical and roentgen-ray evidence of a right lower lobe pneumonitis. Sputa typing was unsuccessful and the pulmonary findings were thought to be a rheumatic pneumonitis. However, we were not certain of this because cold agglutinin determinations to rule out virus pneumonia were not done. There was no rise in nonprotein nitrogen or blood pressure, nor any return

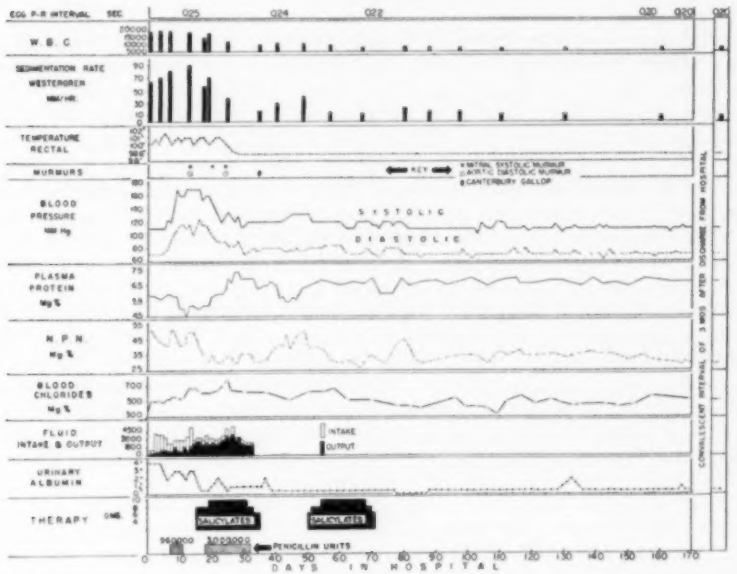

CHART 1.

of the abdominal distention. Inasmuch as the previous administration of penicillin did not produce a beneficial result, it was felt that the continued improvement was due to the sodium salicylate rather than to the penicillin. (Total penicillin, second course, 3,000,000 units intramuscularly in 14 days.)

A transient, harsh, apical systolic murmur was again heard on the twentieth hospital day (fifth day of salicylate therapy, see chart). The patient was now able to take oral feedings, and the blood pressure, nonprotein nitrogen, plasma protein and blood chlorides returned to normal (twenty-fifth hospital day). The previously described murmurs were manifest on the twenty-fourth hospital day, and several days later a Canterbury gallop was heard at Erb's point. The intravenous salicylate therapy was stopped on the thirty-fifth hospital day. During the 20 days of salicylate therapy, the temperature, blood pressure, blood chlorides, plasma protein, non-protein

nitrogen and sedimentation rate had approached normal limits. The gross hematuria had disappeared and the urine showed only a trace of albumin. To ascertain the effects of salicylates, the drug was withheld from the thirty-fifth to the fiftieth hospital days. During this interim the patient appeared clinically well and the temperature and blood pressure remained normal. However, the sedimentation rate and nonprotein nitrogen rose abnormally and the plasma proteins fell below normal. Soon after the readministration of salicylates, these factors returned to normal levels and were so maintained throughout the repeated 20-day period of salicylate therapy. Salicylate withdrawal for the second time (see chart) resulted in a temporary upset of these values. These factors slowly returned to normal and remained so until the day of discharge (one hundred seventieth hospital day).

Comments

The view [1] that some cases of idiopathic nephritis may be instances of rheumatic kidney disease, together with the publications of Berger [7] and Reitman [8] confirming the work of Paul [9] and Rhea,[10] focused our attention on the fact that not only the abdominal muscles and peritoneum but also the kidneys may be involved in rheumatic fever. In Berger's and Reitman's cases, an upper respiratory infection preceded the abdominal signs, which in turn were followed by the clinical manifestations of rheumatic fever. In all instances, these patients responded only to salicylate therapy; thus the marked similarity to our case.

The following criteria were used to establish the diagnosis of rheumatic fever in the case under discussion: acute tonsillitis four weeks prior to the onset of present illness; a four-week latent period preceding the present illness; present illness exhibiting fever with disproportionate tachycardia; leukocytosis; increased sedimentation rate; carditis as evidenced by Canterbury gallop, poor quality of heart sounds, systolic murmur at mitral area, diastolic murmur at aortic area, and prolongation of P-R interval; abdominal distention (rheumatic peritonitis); acute glomerulonephritis; pneumonitis (most probably rheumatic). This case fulfills Swift's [11] Classification of the Rheumatic State, and Jones's [12] major and minor manifestations of the diagnosis of rheumatic fever.

Summary

1. A case is reported of rheumatic glomerulonephritis associated with rheumatic myocarditis, valvulitis, endocarditis, peritonitis, and pneumonitis.

2. References to rheumatic nephritis are rare in the literature. The authors are of the opinion that this condition is a distinct entity which may go undiagnosed, and that some cases of idiopathic nephritis belong in this category.

3. Intravenous sodium salicylate was used successfully in this case only because other established therapeutic methods failed in a critically ill patient. Attention is directed to the lethal dangers of salicylate intoxication and the necessity for judicious use.

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ACUTE PORPHYRIA WITH SPINAL FLUID CHANGES *

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Interest in porphyria has been stimulated of late, by the articles appearing in the literature.[1, 2, 3, 4, 5]

Exhaustive studies of this subject have been made by Dobriner and Rhoads,[1] C. J. Watson,[5] Turner,[2, 6] and many others.[4, 9, 21, 24]

The first description of the disease was made by Hoppe-Selye [7] in 1871. He discovered that the addition of a strong sulfuric acid to hemoglobin produced a substance with a characteristic absorption spectrum which he called "hematoporphyrin." It was discovered later that this was not the substance excreted in the urine and feces of patients who had porphyria. This substance does not exist in nature. Fischer [8] in 1915, by studying a patient with congential porphyria, pointed out the differences between the various porphyrins.

The porphyrins are widely distributed throughout nature. They enter into the formation of such complex molecules as hemoglobin, myoglobin and cytochrome. It is believed that they arise in the body during the synthesis of hemoglobin rather than its destruction, as had been previously assumed.[1, 5, 9, 10] Fischer was one of the first to synthesize the porphyrins, and finally, from them, hemoglobin itself. From these studies he advanced the idea that the porphyrins excreted in porphyria are a product of abnormal synthesis rather than the product of the destruction of hemoglobin. With this idea, Dobriner and Rhoads,[1] Turner,[2, 10] and Waldenström [9] appear to be in agreement. Turner, however, has shown that porphyria may be a persistence of fetal pyrrol metabolism.

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In normal persons, small amounts of porphyrin of the isomeric series I and II are excreted as coproporphyrin I and III in the urine. This has been studied by various investigators,[1, 2, 3, 5, 10, 11, 25] and the excretion has been found to occur in the feces also. In addition, it is believed, but not yet proved, that porphobilinogen is a precursor of the pathologic porphyrin.[25] Porphobilinogen is a colorless substance described by Waldenström,[11] which through the condensation of two molecules forms porphyrin.

In porphyria as well as in a great variety of other diseases these pigments are excreted in amounts far above the normal range.

There is evidence to support the fact that in acute porphyria the abnormal porphyrin metabolism may take place in the liver.[3, 20, 26, 27, 17, 29] Whether hepatic damage is a cause or the effect of porphyria is not known.[3, 25]

The clinical forms of porphyria have been classified into three broad groups: congenital, acute and chronic. While these represent a general classification, some striking variations in the symptoms may be observed, and occasionally the case may present features of more than one group. This variability is noted in many of the cases described in the literature, which present some of the clinical features found in congenital as well as in acute porphyria.

In congenital porphyria the onset is usually early in life but may be delayed until the patient is adolescent. There is a familial tendency. Photosensitivity is prominent, and a chronic bullous or erythematous dermatitis with exacerbations in the spring and summer is present. The urine is Burgundy red at times, with large amounts of coproporphyrin I or uroporphyrin I or III. At autopsy very little may be observed except for a pinkish discoloration of the teeth and bones.

In acute porphyria the attacks are frequently characterized by a sudden onset with severe abdominal pain and obstipation. The symptoms (Waldenström) may be classified into three types: (1) abdominal; (2) nervous; and (3) mental. These may occur singly or in combination. Frequently, the acute attacks are ushered in with the menstrual period, or they may occur postpartum, in females.

It has recently been pointed out [29, 1, 21] that the acute porphyria is as much a familial disease as is congenital porphyria with the underlying mechanism as an inborn error of pigment metabolism.[3, 28, 30] Hypertension and tachycardia are frequent. There is often a low grade fever and leukocytosis may be present. Nervous symptoms such as severe pains and weakness in the extremities, bulbar weakness and a symmetric paralysis of the lower motor neuron type with flaccidity and loss of reflexes may develop.

This acute porphyria may be further classified into (a) acute toxic and (b) acute idiopathic. Both of these types have no fundamental clinical differences; likewise, it has been shown that there are no clinical or laboratory distinctions between the congenital and the acute forms of porphyria. Type I porphyrins are found in both acute and congenital porphyrias and, further, it has been shown that the type III of Waldenström is largely a type I uroporphyrin.[25, 2] In addition, a mixture of the symptomatology of acute and congenital is known to occur together.[16, 17] The toxic and the idio-

pathic forms may be differentiated by eliciting an exciting etiologic agent in the history. Such agents have been described as veronal, nitrobenzol, barbiturates, and trional, sulfonal, sulfonamides, lead, arsenic, the aniline compounds, etc.

The urine is the characteristic phenomenon in the disease; it is the urinary findings that often lead to the diagnosis of obscure cases. In the human, a reddish-brown or a Burgundy-wine colored urine characteristically occurs; this type of urine contains abnormal quantities of pigments. This red urine is the earliest and the most important sign.[3] It may be intermittent or continuous. It may precede other clinical findings by weeks or even years.[3, 5] However, it is to be remembered that sometimes when the patient is observed the characteristic discoloration of the urine may be absent, and the color may not appear unless it stands for a time, or unless exposed either to sunlight or ultra-violet light. The urine may not give a positive test for blood.[11, 5] Also, there are some cases that do not have an abnormal quantity or type of porphyrin in the urine.[12, 22] In these cases one must do an examination of the fecal porphyrins.[13a]

The practical clinical test when the disease is suspected is the Watson-Schwartz urinary test,[13] or exposing to sunlight and allowing to stand, when a dark color will result. Again, an ether soluble fraction of the urine may exhibit fluorescence in ultra-violet light (Wood's light). When uroporphyrin is present in the amounts found abnormally a red fluorescence is observed. Identification can be completed by a spectroscopic examination, and by further physico-chemical methods beyond the scope of the clinician.

The acute porphyrias have been reported on extensively in the literature, together with complete studies in some of the reports, and with descriptions of the various clinical syndromes in over 260 cases.[1, 14, 5, 15] Those cases with neurologic findings have been reported in detail. A review of these cases[3, 4, 25, 14, 15, 16, 23, 29, 23, 34] has revealed that not a single case had shown abnormalities of the spinal fluid. It is believed that the following case is the first to be reported with abnormal spinal fluid findings.

Case Report

A 27 year old white Italian male was admitted on February 15, 1947 in a stuporous and completely disoriented and irrational state. Two weeks before admission he was confined to bed with a severe cold but got up several times during this illness to visit the hospital, where his wife was confined postpartum. Three days before admission, headaches and pain in the back became prominent. Associated with these there were nausea and frequent vomiting. From that time the patient became progressively disoriented and irrational with stupor.

The past history and any other facts that could be obtained were non-contributory. Contact with the private physician who cared for the patient revealed no facts of significance that could contribute to the etiology of the illness.

The family history was completely noncontributory.

The physical examination revealed a well nourished white man who was irrational and entirely disoriented. The patient was drowsy and yet very restless. The temperature was 102° F., the pulse was 82, and the respirations were 28. The blood pressure was 128/72 mm. Hg. The head showed a seborrheic lesion involving the scalp and the skin of the forehead. The ears and mastoid areas were normal. The

pupils were round and regular, but the right pupil was larger than the left. Nuchal rigidity was present. The rest of the physical examination was normal except for the additional neurological findings of diminished abdominal and cremasteric reflexes and bilateral Kernig's sign.

The laboratory studies revealed the following:

A spinal fluid with an initial pressure of 240 mm. H_2O clear fluid. The cell count was 136 per cu. mm. consisting of mononuclear cells. The sugar was 56.0 mg., chlorides 680 mg. and the protein 89.7 mg. Gram-stain and culture were negative for organisms.

A blood non-protein nitrogen was 27.8 mg. An electrocardiogram was within normal limits. The red blood cell count was 5.38 m., hemoglobin 15 gm., white blood cells 8,200, segmenters 67 per cent, lymphocytes 30 per cent, monocytes 3 per cent.

Urinalysis revealed a clear, straw-color fluid with a specific gravity of 1.019. Albumin 2 plus, sugar 3 plus (after infusion 10 per cent glucose in saline), and a microscopic examination of the sediment revealed amorphous material and an occasional red blood cell.

The impression was that the patient had a meningitis, but no antibiotic or chemotherapy was given because no organisms were revealed and polymorphonuclear cells were absent.

Course in the Hospital: On February 16, 1947 a repeat spinal fluid revealed clear fluid with an initial pressure of over 600 mm. water with a 233 cell count per cu. mm. of which 60 per cent were lymphocytes. Sugar was 50 mg.; gram stain was negative for organisms. Culture from the previous day showed no growth.

Urinalysis revealed a clear, light straw-colored urine, with acid reaction and with a specific gravity of 1.007. The albumin was 1 plus, sugar negative. Microscopic revealed amorphous material.

Later in the day the patient passed a bloody-red urine which on analysis revealed an albumin of 4 plus, a negative sugar, and an occult blood of 4 plus, and the microscopic examination revealed a few leukocytes and a few erythrocytes.

It was this urine specimen that led to the diagnosis. A Watson-Schwartz test [13] was performed and the urine was found positive for porphyrins (a red reaction with paradimethylaminobenzaldehyde insoluble in chloroform). The diagnosis was then established as an acute porphyria.

Intravenous fluids, oral fluids and vitamins were administered. No other medications were given.

On February 20 the patient was afebrile, clear and alert, and his neurological signs had disappeared.

By February 24 the patient was ambulatory and had no complaints. The temperature was still normal.

The urine showed a slight trace by the Watson-Schwartz test for porphyrins but no other abnormalities; its color was straw-yellow.

The patient was discharged on February 25, the tenth hospital day. The urine was negative on this day by the Watson-Schwartz test for porphyrins.

Since his discharge there has been no further red urine or recurrence of his symptoms. There is no suggestion of the disease in any other member of his family. This information was obtained by letter from the patient on November 11, 1947, approximately nine months after his illness. No members of the family were available for examinations.

Discusssion

This case is apparently the first acute porphyria with spinal fluid abnormalities to be reported in the literature. It is to be classified as an idiopathic type,

since no etiological factor could be determined. The fact that spinal fluid abnormalities may occur in this disease is worthy of emphasis since it signifies that acute porphyria must be considered in the differential diagnosis of neurological diseases with similar spinal fluid changes.

The great majority of the cases of porphyria that exhibit central nervous system signs resemble an ascending paralysis of Landry. The clinical pictures have been well described in previous literature.[3, 14, 15] However, not a single instance of the reported cases revealed any abnormality of the spinal fluid.[3, 14, 15, 16, 18] The finding of porphyrins in the spinal fluid has been described by Prunty.[16] The cases observed at the Boston City Hospital and the Massachusetts General Hospital showed no changes in the cerebrospinal fluid, except for one which had a slightly elevated protein in the spinal fluid.[18, 19] This is explained by the fact that fatal cases do not show any inflammatory reaction in the meninges.[16]

The underlying mechanism of the production of the symptoms has been described at length in various publications stressing the dispersion of the pigment into the cell, vasoconstriction and ischemic theories.[1, 3, 5, 14, 15, 20, 21, 22, 23] For extensive reviews the references should be consulted.

The mortality in cases of acute porphyria with nervous system changes is high (between 50 and 75 per cent).[15, 3, 22, 23, 24]

It must be postulated that the spinal fluid abnormalities found in this case were due to some meningeal involvement. It is unfortunate that the spinal fluid was not examined for the presence of porphyrins.

It might be considered that some virus meningo-encephalitis (e.g., acute lymphocytic choriomeningitis) process was present, which in turn gave rise to the acute porphyria or produced an exacerbation of a "latent" porphyria. However, past experience and the prompt recovery of this patient do not lead one to believe that this was the case. Besides, porphyrins are no longer present in his urine. It is conceivable that in some way the abnormal porphyrins produced a reaction in the meninges either by vascular effects, e.g., ischemia, or by direct cellular irritation; however, this does not appear to occur often if it occurs at all.[25, 1, 3, 14]

It is interesting to note that this patient exhibited no hypertension and had no abdominal complaints previous to the onset or during the course of the illness. Diminished reflexes are characteristic of the peripheral nerve involvement that occurs in this disease. However, they were absent in this instance.

Summary

1. A discussion of porphyria is presented and reference is made to the extensive reviews on the subject.

2. A case of acute idiopathic porphyria is presented with spinal fluid abnormalities. There are no reported instances of such changes of the spinal fluid in cases with neurological findings. It is believed that these changes were due to the abnormal porphyrins affecting the meninges; however, other possibilities have been mentioned. The importance of this finding in differential diagnosis is emphasized.

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EXTREMELY HIGH LYMPHOCYTE COUNT IN LYMPHATIC LEUKEMIA: REPORT OF A CASE*

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Several cases of leukemia demonstrating white cell counts as high as 1,000,000 have been reported. According to Forkner,[1] "the actual number of leukocytes may vary from a few thousand to a million per cu. mm. of blood." Patients with myeloid leukemia and white blood counts approaching 1,000,000 have been seen at the Cleveland Clinic, but we have found no reference to cases with a white cell count of over 2,000,000, such as the one here presented.

Case Report

A white man, aged 53, was admitted to the Cleveland Clinic on February 28, 1938, complaining of "gas" in the abdomen, aching pain in the left side and back, headache, dizziness, failing vision, progressive weakness, and loss of 20 pounds in weight. His complaints had become increasingly severe during the past six months. The abdominal distress was unrelated to meals, but after eating he felt "full." Bowel habits were unchanged, but recently the stools had become light-colored. Headache had been constant and usually limited to the frontal region. Dizziness caused him to stagger so that he frequently required support. On one occasion he had fainted, this attack being followed by nausea and vomiting. His vision had been failing so that he could no longer read, even with his glasses. He was disturbed by "spots" floating before his eyes.

Family history was irrelevant, and he had had no previous illness since childhood.

Physical examination disclosed a well-developed man weighing 203 pounds. The temperature was normal, the blood pressure 138 mm. Hg systolic and 100 diastolic. Examination of the cardiovascular, genitourinary, and respiratory systems was negative, and the chest was normal on roentgenologic examination.

There was generalized moderate enlargement of superficial lymph nodes, and the spleen was tender and enlarged to below the umbilicus. The liver also was slightly enlarged. Hearing was diminished and the tonsils were large and cryptic.

Eye examination showed normal light reactions. The outlines of the discs could not be distinguished clearly because of edema which extended well out into the retinas. The veins were markedly distended and the arteries slightly constricted. Many old

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and new hemorrhages were present throughout the fundi, and there was macular damage. Fine floating opacities were observed. Vision of the left eye was 6/60 and of the right eye 3/60. Visual fields showed relative central scotoma and moderate loss for color. These eye symptoms were interpreted as typical of leukemia.

Blood Wassermann reaction was negative, and routine blood chemistry and urine examinations were normal. The white blood counts showed 2,300,000 cells per cu. mm., most of which were mature lymphocytes. This count was checked several times. The red cell count was 2,710,000 per cu. mm., hemoglobin 52 per cent (8 gm. per 100 c.c.), and the color index 0.96. Sternal puncture was refused.

Roentgen-ray therapy was given by the "body spray" method, using 200 kv. and filter equivalent to 1.4 mm. hvl. cu. at 100 cm. distance. The spleen also was irradiated. The patient tolerated treatment very well, and within 10 days a total of 300 r had been given by spray to the body anteriorly and posteriorly and 200 r to the spleen. Two weeks after this course of treatment the white cell count was 1,700,000 and a week later 1,050,000, 65 per cent of the cells being lymphocytes. The lymph nodes and spleen decreased somewhat in size. The patient was also given blood transfusions.

During the next year roentgen-ray therapy was given at intervals. The lowest white cell count was 137,000. At one time the patient developed several small, painless, movable nodules in the skin of his legs. The surface skin was normal over all except one nodule, about 3 cm. in diameter, on the left lower leg. The skin over this was deep brown, and the mass fluctuated. On aspiration, 1.0 c.c. of blood-tinged viscous fluid was withdrawn. This proved to be sterile.

The patient became progressively more anemic, and in spite of blood transfusions the red cell count fell to 1,380,000 and the hemoglobin to 33 per cent; color index was 1.17. The white blood count at this time was 205,000 cells, 56 per cent of which were lymphocytes. He died 23 months after admission.

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SPONTANEOUS HEMOPNEUMOTHORAX: REPORT OF TWO CASES *

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Spontaneous hemopneumothorax is a relatively rare disease. Approximately 60 cases had been reported through 1947. Within a three-month period, however, two cases were seen at this hospital. The immediate treatment of this entity is so important that its prompt recognition becomes imperative. In view of the newer knowledge relative to hemothorax gained during the last war, it is felt that the pathogenesis and the therapeutic implications of the disease need further emphasis.

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From the Veterans Administration Hospital, Newington, Connecticut, and the Department of Medicine, Yale University School of Medicine.

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Case Reports

Case 1. A 22 year old letter carrier was admitted to the hospital on the evening of August 23, 1947, with chief complaints of pain in the right chest and epigastrium, and shortness of breath. Several hours earlier, while sitting quietly in a chair, he had experienced sudden, sharp, severe pain, aggravated by deep inspiration. Because of increasing discomfort and mild dyspnea he was seen by his family physician, who sent him into the hospital.

In July, 1945, while in the Navy, he had experienced a similar episode of right chest pain. His chest was strapped with adhesive tape with complete relief of symptoms in four days. The past history was otherwise negative.

The patient was a well developed, tall, thin white male in considerable pain and moderate respiratory distress. The rectal temperature was 97.6° F., the pulse rate 76, the respiratory rate 36, and the blood pressure 110 mm. Hg systolic and 60 diastolic. The respirations were shallow, and slight cyanosis of the lips was present. The trachea was deviated slightly to the left, and there was considerable splinting of the thorax, particularly on the right. The right chest was hyper-resonant, and breath sounds were absent except over the upper thorax posteriorly, where they could be heard faintly. The heart was shifted slightly to the left. There was no abdominal tenderness, but the patient complained of right chest pain on abdominal palpation. The remainder of the physical examination was within normal limits.

A diagnosis of spontaneous pneumothorax was made and confirmed by fluoroscopy. The right lung was approximately 50 per cent collapsed, and there was minimal displacement of the mediastinal contents to the left. Codeine, 60.0 mg. subcutaneously, was given with considerable relief of pain. Oxygen was administered within a tent and the cyanosis cleared rapidly. The patient spent a comfortable night. When seen the following morning, he was in a state of shock. The skin and mucous membranes were pallid, the blood pressure was 74 systolic and 44 diastolic, and the pulse rate was 120. Examination revealed signs of a hydropneumothorax on the right, with the trachea and heart shifted markedly to the left. A diagnostic thoracentesis yielded 50 c.c. of dark red fluid under pressure, with erythrocyte and hemoglobin values identical with those of the circulating blood. He was given 60.0 mg. of codeine and 500 c.c. of plasma immediately. The red blood cell count was 3,050,000 per cu. mm. and the hemoglobin 8.3 gm. The white blood cell count was 11,050, with 81 per cent neutrophiles. The bleeding and clotting times were normal.

Following the plasma, 1,000 c.c. of whole blood were given. The blood pressure rose promptly to normal, and the patient showed marked symptomatic improvement. Shortly after the transfusion, the red blood cell count was 2,810,000 and the hemoglobin 7.0 gm. Bedside roentgen-ray of the chest revealed a right hydropneumothorax with complete collapse of the lung and the fluid level at the third interspace anteriorly (figure 1). There was marked displacement of the mediastinal contents to the left.

Three thoracenteses during the next 30 hours yielded a total of 2,460 c.c. of dark blood. During this period 2,500 c.c. of whole blood, 500 c.c. of plasma, and 1,000 c.c. of 5 per cent dextrose in saline were given intravenously. The red blood cell count rose to 3,480,000 and the hemoglobin to 8.9 gm.

After the initial period of improvement, the patient began to have frequent episodes of cyanosis and chest pain which required morphine for relief. Repeated determinations of intrapleural pressures showed no appreciable fluctuation. The respiratory rate persisted at 38 to 40. The blood pressure ranged between 140 and 172 systolic and 48 to 80 diastolic. The pulse rate varied between 80 and 120 and the temperature between 102° F. and 102.8° F., rectally.

The patient was given 50,000 units of penicillin intramuscularly every three

hours, and 100,000 units were instilled into the chest cavity after each thoracentesis. Following the removal of approximately 2,000 c.c. of blood and 500 c.c. of air, roentgen-ray revealed considerable reëxpansion of the lung and the presence of a moderate amount of fluid.

Because of the relative stability of the blood pressure, the pulse rate, and the erythrocyte and hemoglobin values, on repeated examinations, it appeared that there was no further bleeding into the right pleural space. Physical examination disclosed a shift of the mediastinal contents toward their normal position and a reduction in the fluid on the right.

FIG. 1.

Although bleeding had apparently ceased, the patient's condition grew worse during the evening of the third hospital day. The temperature continued to rise, as did the pulse rate. The white cell count was 10,700, with 82 per cent neutrophiles. The patient became disoriented, began to raise frothy, white sputum, and suddenly died on the fourth hospital day. Approximately five minutes before death the blood pressure was 170 systolic and 40 diastolic, and the temperature was 105° F., rectally. Immediately after death, thoracentesis yielded only a few cubic centimeters of dark red blood. The clinical course is charted in figure 2.

Autopsy. There were approximately 500 c.c. of clear yellow fluid in the left pleural cavity. No adhesions were found. The right lung was expanded and filled most of the hemithorax. The pleural cavity contained 250 c.c. of clotted blood, and 175 c.c. of dark red, fluid blood with a hemoglobin value of 11.7 gm. No intact adhesions were present. The right visceral and parietal pleurae were covered with numerous petechial hemorrhages. At the apex of the right thoracic cavity there was a thrombus firmly attached to the chest wall. After block removal of this area it was noted that only a few millimeters of parietal pleura and adhesions separated the thrombus from a large vein (10 mm. in diameter). Several of its branches coursed around the clot, but no continuity could be demonstrated grossly.

In the apex of the right lung was an area of scarring and fibrosis, with one fibrous adhesive band, measuring approximately 2 mm. by 7 mm., which apparently had been torn away from the parietal pleura at the point where the thrombus was found. Compression of the lung below the apex produced oozing of blood through a pin point opening in the center of the adhesion. There were considerable congestion and edema of both lungs, particularly the right. The bronchial tree was filled with frothy, serous fluid.

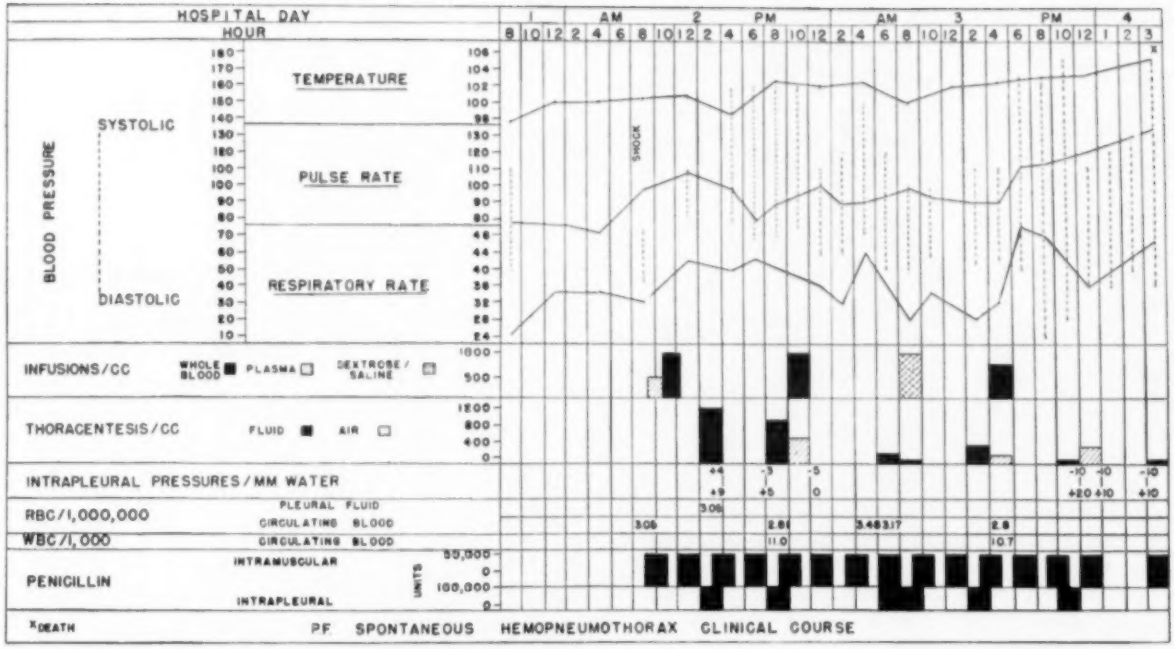
Histologic study revealed large amounts of pink-staining edema fluid in the alveolar spaces. In one area of the right lung red blood cells were also present, and the surrounding alveoli were compressed and atelectatic. Scattered foci of polymorphonuclear leukocytes were also present in the edematous areas. A section through the parietal pleura of the right apex showed a large vein in the subpleural tissue. The pleural lining cells were swollen and cuboidal, and the underlying tissue, which was edematous and congested, contained numerous lymphocytes and scattered eosinophiles. Attached to the pleural surface and overlying the vein already described was a large, irregular thrombus consisting chiefly of platelet lamellae and red cells. There was early fibroblastic organization at the margin of attachment.

The remainder of the gross and microscopic examination was not remarkable. Permission to examine the brain was not obtained. The anatomical diagnoses were: (1) ruptured pleural adhesion, apical, right; (2) hemopneumothorax, right; (3) pulmonary congestion, hemorrhage, and edema; (4) bronchopneumonia, focal; (5) hydrothorax, left.

Comment. This case illustrates the necessity for close observation of all patients with spontaneous pneumothorax. In retrospect, it is felt that the diagnosis of hemothorax would have been made earlier if the vital signs had been recorded more frequently than every four hours. Prolonged, untreated shock may be the explanation of the ultimate failure of treatment, despite cessation of bleeding and the prompt return of blood pressure to normal after the administration of blood in an amount greater than that aspirated. In view of the relatively normal intrapleural pressures on repeated determinations, marked fluctuation in intrathoracic dynamics seems not to have been present.

The exact cause of death was not apparent at autopsy. There was no evidence of overwhelming sepsis. It is unfortunate that the brain could not be examined, because the terminal rise in temperature and the wide variations in pulse pressure suggested damage of the hypothalamus. Of interest is the fact that the site of bleeding was demonstrated unequivocally.

Case 2. A 21 year old premedical student entered the hospital on October 29, 1947, with chief complaints of chest pain, shortness of breath, nausea, and vomiting. Three days prior to admission, while sitting in class, he experienced sudden, sharp pain in the left chest associated with mild dyspnea. He went to the school dispensary,


HOSPITAL DAY
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DEXTROSE / SALINE
THORACENTESIS/CC
FLUID
AIR
INTRAPLEURAL PRESSURES/MM WATER
RBC/1,000,000
PLEURAL FLUID
CIRCULATING BLOOD
WBC/1,000
CIRCULATING BLOOD
PENICILLIN
INTRAMUSCULAR
INTRAPLEURAL
UNITS
XDEATH
PF SPONTANEOUS HEMOPNEUMOTHORAX CLINICAL COURSE

FIG. 2.

was given some "pills" by the school nurse, and was later put to bed because of continued discomfort. He was seen by a physician the following day and his left chest was immobilized with adhesive tape. The next day, roentgen-ray of the chest at a local hospital revealed "collapse of the left lung." The respiratory distress continued,

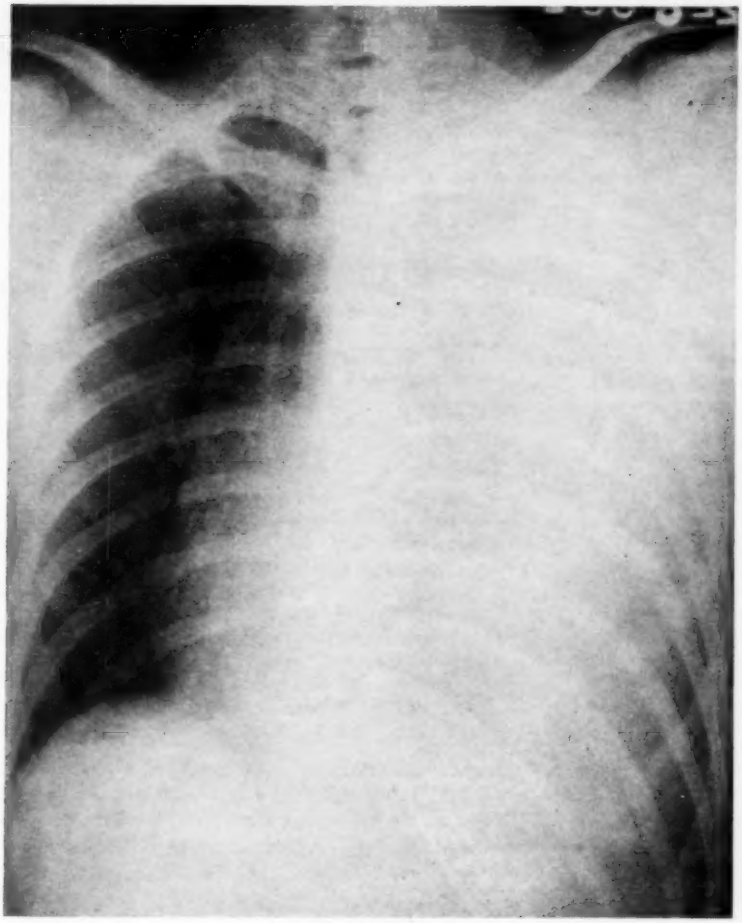

FIG. 3.

and on the third day the patient developed nausea and vomiting. He was then transferred to this hospital. The past history was completely negative for tuberculosis or other pulmonary disease.

The patient was a somewhat thin white male in obvious shock. He was retching and complaining of chest pain. The sensorium was clouded; the skin and mucous

membranes were blanched; the extremities were cool distally. The pulses were almost imperceptible. The temperature was 100.4° F. rectally, the heart rate 148, the respiratory rate 24, and the blood pressure 96 systolic and 40 diastolic. The intercostal spaces on the left were obliterated, and the respiratory excursions were markedly decreased on that side. The left upper lung fields were hyperresonant anteriorly and posteriorly with greatly diminished fremitus. There were flatness and absent fremitus over the left lower chest posteriorly and laterally. No breath sounds were heard

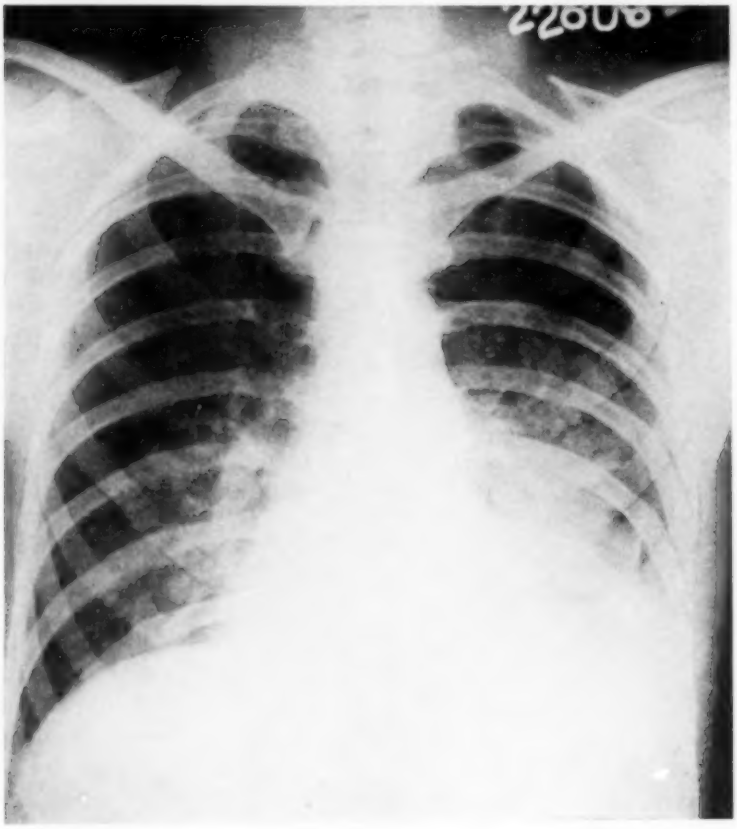

FIG. 4.

over the entire left hemithorax. The heart was displaced markedly to the right. The remainder of the physical examination was negative.

The physical signs of hydropneumothorax and exsanguination suggested a massive hemopneumothorax. The patient's condition was critical, and transfusion of type "O," Rh-negative blood, preceded by sodium bicarbonate intravenously, was started. Positive pressure helium and oxygen mixture was also administered at once. A roentgenogram, taken with the patient recumbent, revealed a homogeneous density

completely obscuring the left hemithorax (figure 3). There was marked displacement of the trachea and heart to the right. Examination of the blood disclosed an erythrocyte count of 2,820,000 and 8.2 gm. of hemoglobin. The white cell count was 27,400, with 84 per cent neutrophiles.

After the patient had received approximately 200 c.c. of blood the blood pressure rose, the sensorium cleared, and the nausea subsided. A total of 1,000 c.c. of whole blood was given initially, and a thoracentesis was then performed. Approximately 900 c.c. of dark red blood, with erythrocyte and hemoglobin values of 3,770,000 and 10.5 gm., respectively, were removed. The intrapleural pressures, determined at the third interspace anteriorly, were plus 2, plus 5 after the procedure.

The blood pressure thereafter remained within normal limits, although the pulse rate continued elevated for the first two days. Multiple thoracenteses during the first three days yielded a total of 4,900 c.c. of bloody fluid, with erythrocyte and hemoglobin values which steadily declined. A total of 4,000 c.c. of whole blood was given in the first three days. Thereafter, repeated blood cell counts were within normal limits.

As prophylaxis against infection, the patient received 50,000 units of penicillin intramuscularly every three hours and 100,000 units intrapleurally after each thoracentesis. Cultures of the pleural fluid yielded no growth.

The patient had few complaints after the first day. He had very little pain and no dyspnea after the initial thoracentesis. Positive pressure helium and oxygen therapy was continued for one week. Low-grade fever persisted until the twentieth day. Supervised breathing exercises were begun on the fifth day, and expansion of the left chest rapidly returned to normal.

Serial roentgenograms of the chest revealed progressive improvement. On the third day there was considerable decrease in the amount of fluid, and the apex of the lung was at the level of the fifth posterior rib (figure 4). The mediastinal contents had returned to nearly normal position. On the twelfth day examination showed almost complete reëxpansion of the lung, with pleural thickening over the left apex.

Tuberculin tests in the first and second strengths were negative, and examinations of three 24-hour sputum specimens revealed no acid-fast bacilli.

The patient was asymptomatic at time of discharge from the hospital on December 1, 1947, the thirty-third hospital day. The clinical course is presented in figure 5.

On follow-up examination six weeks later the patient had no complaints. Examination of the chest revealed no abnormalities. The vital capacity, blood cell counts, and sedimentation rate were all within normal limits. Roentgenogram revealed minimal residual pleural thickening (figure 6).

Comment. This case also emphasizes the importance of making an early diagnosis of hemothorax as a complication of spontaneous pneumothorax. The patient was referred to this hospital with the diagnosis of "massive pleural effusion complicating collapse of the lung." His course was uneventful after energetic treatment was instituted.

Discussion

In the cases of spontaneous hemopneumothorax reported up to 1948 there was a mortality of approximately 30 per cent. Postmortem data were available in 14 cases and histologic studies in five.[1] In many instances the site of bleeding was not demonstrated, but ruptured emphysematous bullae and torn adhesions were common findings. It is significant that definite tuberculosis was rarely present.

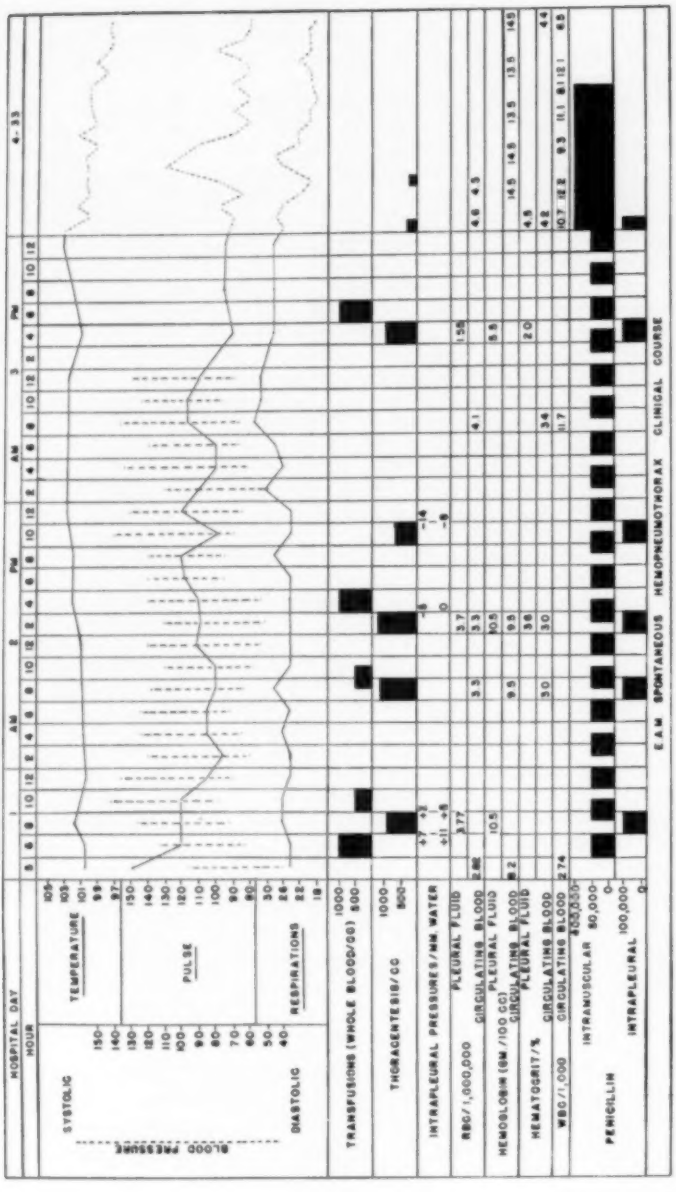
HOSPITAL DAY
HOUR
BLOOD PRESSURE
SYSTOLIC
DIASTOLIC
TEMPERATURE
PULSE
RESPIRATIONS
TRANSFUSIONS (WHOLE BLOOD/GC)
THORACENTESIS/CC
INTRAPLEURAL PRESSURES/MM. WATER
RBC/1,000,000
PLEURAL FLUID
CIRCULATING BLOOD
HEMOGLOBIN (GM./100 CC)
HEMATOCRIT/%
WBC/1,000
PENICILLIN
INTRAMUSCULAR
INTRAPLEURAL
E.A.M. SPONTANEOUS HEMOPNEUMOTHORAX CLINICAL COURSE

FIG. 5.

Hemothorax, though rare, is a potential complication in every case of spontaneous pneumothorax. In many cases there is an appreciable time interval of several hours to days between the initial symptoms and the signs and symptoms of intrathoracic bleeding. All cases of simple pneumothorax deserve continued observation. Adhesions which limit the extent of an initial collapse may

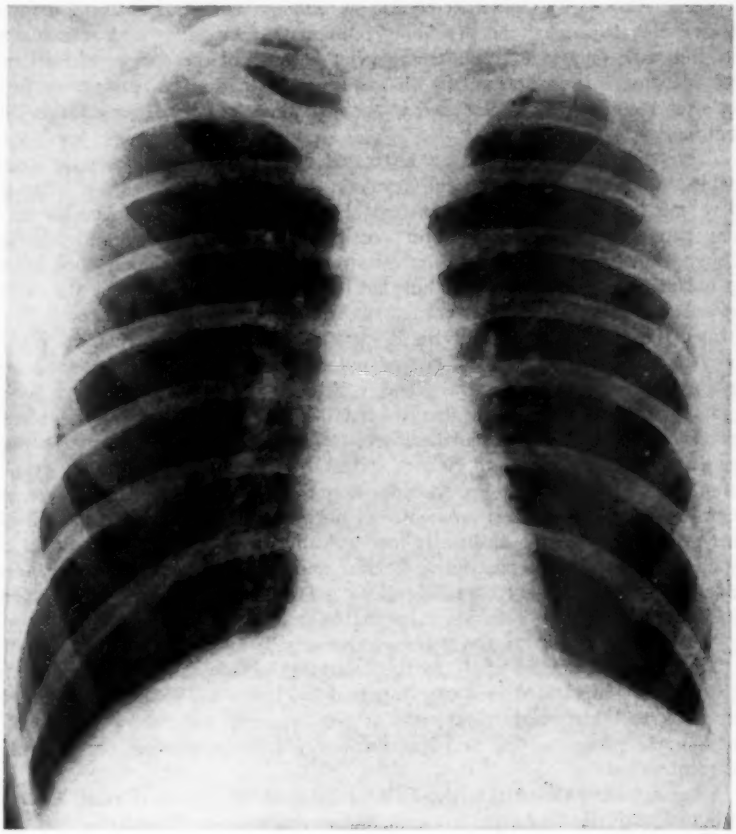

FIG. 6.

subsequently rupture and bleed. More widespread awareness of this problem would undoubtedly decrease the mortality, since loss of time in the institution of treatment may be disastrous.

The principles of treatment of hemothorax have been clarified during the past five years. In 1942 Hartzell,[2] in a comprehensive review, stated that

thoracentesis was inadvisable except for diagnosis and for the correction of marked mediastinal displacement. Rapid and complete evacuation of blood, especially without air replacement, was cited as a dangerous procedure because of the likelihood of renewed bleeding secondary to reduction in intrapleural pressure. The hazards of sudden alterations in intrathoracic pressure relationships were also stressed. The late effects of hemothorax were not considered important, since it was felt that clotting was insignificant and absorption rapid. Hartzell also expressed the prevailing opinion that infusions and transfusions were indicated only in extreme emergencies because of the danger of initiating fresh bleeding. It is noteworthy that specific evaluation of respiratory function after recovery is not recorded in most of the cases treated with this conservative regimen.

These dicta, which have been reiterated as late as 1946,[2, 4] are no longer tenable, and a major change in viewpoint has been expressed by Waring.[5] There can be no doubt that persistent shock, clinical or subclinical, is much more dangerous that the doubtful possibility of starting renewed bleeding through transfusion therapy. Furthermore, it is clear that blood does indeed clot normally in the pleural space but that it is rapidly defibrinated by the churning action of respiratory and cardiac movements. Melick and Spooner[6] reaffirmed this fact experimentally in 1945. They also observed that the pleural cavity readily absorbs blood. Sellors,[7] on the basis of serial determinations of the fibrinogen content of pleural blood, concluded further that an active serous exudate is produced which enhances the deposition of fibrin on the pleural surfaces. It is not justifiable, therefore, to depend on absorption in the management of hemothorax, and Sellors states: "The essence of recovery from a hemothorax is that the lungs should reach the chest wall and obliterate any pleural cavity at the earliest moment. If fibrin develops before the pleural layers become apposed, the closure is mechanically delayed. Once the fibrin has organized, it acts as a constricting barrier and encourages persistence of dead space. The risk of fibrothorax develops. This means full respiratory function is not recovered. This is the inevitable state of affairs in hemothoraces of appreciable size which are treated conservatively."

That these principles apply to the treatment of spontaneous hemopneumothorax is well illustrated in a case reported by Jones and Gilbert.[8] Death occurred on the thirty-eighth day, and at post mortem there were 4,000 c.c. of blood in the pleural cavity and massive fibrin deposits causing obstruction of the great vessels.

Samson[9] emphasized that the bulk of delayed surgery performed after intrathoracic injuries sustained in the last war was concerned with the complications of hemothorax, i.e., clotting, organization, and infection. He pointed out that the rate of infection was increased in those cases which were not aspirated promptly and completely, and that infection accelerates the speed with which organization takes place. The principle of rapid reëxpansion of the lung reduced the infection rate from 25 per cent to 7 per cent in the Mediterranean Theater.

These authors[5, 7, 9] stated further that fear of renewed bleeding and profound fluctuation in pressure relationships secondary to evacuation of blood is

groundless when ordinary care is exercised. They also emphasized that air replacement defeats the primary purposes of evacuation through its irritative effects and its creation of dead space.

It is apparent that the problem in spontaneous hemopneumothorax differs in some respects from that in traumatic hemopneumothorax. In the latter, tissue injury is usually more extensive and the danger of infection and organization correspondingly greater. The principles of treatment, however, are the same in each.

Summary

1. Two cases of spontaneous hemopneumothorax are presented.

2. The importance of considering hemothorax a potential complication of simple spontaneous pneumothorax is stressed.

3. The principles of treatment, i.e., prompt restoration of the circulating blood volume, and rapid evacuation of blood and reëxpansion of the lung, are emphasized.

Addendum

Since this report was submitted, two additional cases of spontaneous hemopneumothorax have been treated in this hospital. Both made complete recoveries with aspiration, transfusion and antibiotic therapy as described above. One patient required 1,000 c.c. and the other 2,000 c.c. of blood for replacement. In the first instance 1,750 c.c. and in the second 2,850 c.c. of bloody fluid were aspirated from the chest. Both patients had negative work-ups for tuberculosis.

A third patient had had a spontaneous hemopneumothorax in 1944 which had been treated with closed catheter drainage. On admission in February 1949, he complained of severe exertional dyspnea and was found to have a massive fibrothorax. Decortication of the lung was performed, following which the patient's symptoms cleared. This case emphasizes the need for early and energetic treatment of spontaneous hemopneumothorax if late complications are to be avoided.

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AN UNUSUAL RETROPERITONEAL CYST SIMULATING A CALCIFIED HEPATIC CYST *

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TUMORS of the upper abdomen frequently present a problem in diagnosis. We are presenting such a case because, in addition to the many interesting physical findings, the diagnosis could not be made before operation. It is felt that this patient will serve to illustrate an unusual problem in differential diagnosis when the explanation of upper abdominal tumors is considered.

CASE REPORT

A 63 year old white female entered the University Hospital on April 12, 1948, complaining of swelling of the abdomen and lower extremities. She had been well until 1943, when she first noticed swelling of the abdomen. This swelling was slowly progressive until admission. For two years before admission she had noticed progressive weakness and ease of fatigue. Shortly before admission there was pain in the right upper quadrant which was produced by any jarring motion. For four years the patient had had typical gall bladder symptoms characterized by anorexia, epigastric fullness, dyspepsia, and nausea, but no vomiting. These were precipitated by fried and fatty foods, cabbage, lettuce, and especially over-eating, and were intensified during the month prior to admission. She had never noticed jaundice, or bloody, tarry, or clay-colored stools. For four weeks the patient had observed edema and petechiae of the lower extremities. The swelling was aggravated by standing and relieved by assuming the supine position. She had had no chills, fever, or night sweats. She was sent to the hospital with the diagnosis of "liver trouble."

The family history was suggestive of hypertension but was otherwise not remarkable. The past history was non-contributory. The systemic review revealed that she had had hypertension since 1943, accompanied by dyspnea on climbing one flight of stairs; nocturia and dysuria for the past year, and arthralgia in both knees for the past two years. Later questioning brought out that the patient had lived on a sheep farm for 10 years prior to admission and harvested and worked with raw wool, and was in close contact with dogs reported to have killed sheep.

Physical Examination: Height 5 feet 4 inches; weight 150 lbs. (usual weight 155 lbs.). The patient was well developed but poorly nourished and appeared chronically ill. The skin had purpuric spots on the right thigh and the left knee and was generally atrophic. There was no palpable lymphadenopathy. The pupils were round, equal and active; there was grade III hypertensive retinopathy without hemorrhages or exudates. There was a pulsatile supraclavicular mass on the right. No other abnormalities were found in the neck. The thorax was symmetrical but there was an increased anteroposterior diameter. The lungs were clear and the diaphragms moved freely. The heart was not enlarged and there were no irregularities or murmurs. Blood pressure 205/122 mm. of mercury. The breasts were normal. The abdomen was distended; the costoaxillary, thoracoepigastric, superficial epigastric, and superficial circumflex iliac veins were visibly engorged bilaterally (figure 1). The paraumbilical veins were not visible, but were demonstrably engorged by infrared photography (figure 2). There was a protruding mass occupying both upper

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FIG. 1. The engorged veins of the flank are photographed from the patient's right. The abdominal mass can also be seen.

FIG. 2. An infra-red photograph to show engorgement of the paraumbilical veins.

quadrants, extending below the umbilicus on the right and arching upward to the left costal margin in the anterior axillary line. The edge was sharp and smooth. The entire mass was firm and tender. The tip of the spleen was palpated by one observer but not by several others. There was no fluid wave or shifting dullness. No other masses or tenderness were detected. Rectal and sigmoidoscopic examinations were normal. Vaginal examination was negative. There was bilateral ankle and pretibial pitting edema. There was no edema of the upper extremities but there was

FIG. 3. Lateral roentgen-ray to show the calcified wall of the mass. Multiple small biliary calculi are designated by arrows. The shadow of liver tissue can be seen anterior to the mass. Calcified plaques in the aorta can be seen just above the iliac crest and posterior to the mass.

pitting edema over the sacrum. The peripheral arteries were characteristic of Mönckeberg's sclerosis. The neurological examination was not remarkable.

Laboratory Findings: The urine was found to contain one plus albumin and occasional white blood cells and red blood cells. The specific gravity was 1.020. The stool did not contain ova, parasites, or blood. The Kahn test was negative. The complete blood count was characterized by a hemoglobin of 9.0 gm., a red blood count of 3.6 millions and a white blood count of 5,750. The differential count was normal.

The hematocrit was 31.5. There was some variation in size and shape of the red blood cells. The cephalin-cholesterol flocculation was negative. The serum bilirubin was not elevated. There was no retention of bromsulfalein. The total serum proteins were 5.8 gm. per cent with an A/G ratio of 2:1. The prothrombin time was normal. The plasma cholesterol was 107 mg. per 100 c.c., with 72 per cent of esters. The electrocardiogram revealed slight left axis deviation with inverted T waves in

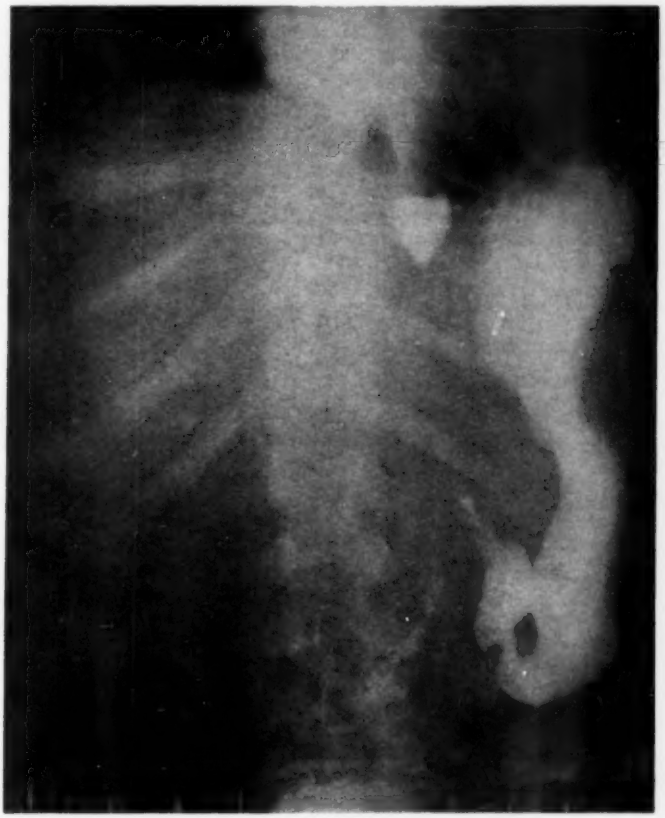

FIG. 4. Anteroposterior roentgen-ray showing the stomach and duodenum filled with barium and displaced to the left. The calcified wall of the mass can be seen, but not as well as in figure 3. The collection of barium above the left hemidiaphragm may represent a phrenic ampulla or a small hiatus hernia.

Lead I, suggesting myocardial changes. The echinococcus skin test and complement fixation test were negative. The complement fixation for *E. histolytica* was negative, and an old tuberculin skin test was negative in 1/100 dilution. The femoral venous pressure was 325 mm. of H_2O (normal 120 mm. of H_2O). The brachial venous pressure taken simultaneously was 80 mm. of H_2O (normal).

Roentgen-Rays: Examination of the gastrointestinal tract revealed a very large globular mass outlined by narrow, calcified peripheral margins. The stomach was displaced to the left. The gall bladder was not visualized but showed many small biliary calculi. The liver shadow was anterior to the right upper quadrant mass. There was also calcification in the wall of the abdominal aorta (figures 3 and 4). The chest roentgen-ray was negative.

FIG. 5. Postoperative lipiodol visualization, showing the decrease in size of the cavity of the mass and the return of the liver to its normal position.

Course in Hospital: The course in the hospital was uneventful and the patient was transferred to surgery with a presumptive diagnosis of echinococcus cyst of the liver, in spite of the negative skin and complement fixation tests. She received five 500 c.c. transfusions of whole blood in preparation for incision, drainage, and marsupialization of an abdominal cyst. At operation the cyst was found to be retroperitoneal and displacing the liver to the left and almost across the midline. The cyst was aspirated and an estimated 3,500 c.c. of greenish brown fluid removed. After

aspiration the liver returned to its normal position. The cyst wall was calcified and was about one-half inch thick. A marsupialization was done and the wound drained a brownish fluid throughout her hospital stay. Lipiodol was injected and showed some decrease in the size of the cyst (figure 5). Her convalescence was marked by one episode of bronchopneumonia and by intermittent temperature elevations, the latter being thought to be due to infection within the cyst. She received penicillin both intramuscularly and as irrigations and was discharged afebrile on the twenty-second postoperative day, the edema of the lower extremities having disappeared.

Pathology Report: Tissue of the cyst wall and contents was interpreted by A. J. French, M.D., Associate Professor of Pathology, University of Michigan Hospital, as follows: "This specimen is interpreted as an aneurysm in an artery showing advanced calcific atherosclerosis and mural thrombosis."

Additional sections of the cyst wall and contents were examined by Carl V. Weller, M.D., Chairman of the Department of Pathology, University of Michigan Hospital, and interpreted as follows: "Most of this material is old blood such as might come from the interior of an aneurysm or from any hematoma. The vessel wall is imperfectly represented, and it is impossible to form an opinion as to whether this represents a saccular aneurysm or an encapsulated hematoma which has developed in a dissecting aneurysm." (Figure 6.)

The total proteins of the cystic fluid were 5.5 gm. per cent with A/G ratio 1:2, and the cystic fluid contained a trace of amylase.

Discussion

This case presented the classical features of obstruction of the inferior vena cava as described by Ferris and Blankenhorn.[1] The presence of increased pressure in the femoral, normal pressure in the brachial and visible congestion of the flank veins pointed to a solitary abscess or cyst of the liver.[1, 2, 3] The fact that portal obstruction also existed did not necessarily contradict this.[1] The afebrile course, when coupled with the history of contact with sheep-killing dogs,[4, 5] seemed to rule against an abscess. The skin and complement fixation tests were negative but several authors [6, 7, 8] have shown that this may occur in an appreciable number of cases with proved echinococcus disease. Berk [9] as well as Pleasants [3] emphasizes the likelihood that the *Taenia echinococcus* is the etiological agent in solitary cysts of the liver.

There have been many reports of retroperitoneal tumors, cysts, and aneurysms of the abdominal aorta and hepatic artery,[10, 11, 12, 13, 14, 15, 16] but we could find no reported case that so closely simulated a solitary cyst of the liver.

Hafezi,[17] in a study of retroperitoneal cysts, has emphasized that there are no characteristic symptoms and signs, no definite regular site, and that they are relatively rare. They occur more commonly in females, 10 to three, and are seen in all age groups.

Retroperitoneal cysts in reference to symptoms were divided into three classes by Moynihan in 1897. The first class was the cyst which has no symptoms and is discovered accidentally at autopsy or on a routine examination. The second class presents a chronic course and manifests itself as an abdominal mass which may produce pain, indigestion, and constipation. Acute pain may be associated with bleeding into the cyst, with a rapid increase in size of the cyst. The third class produces acute abdominal symptoms by causing intesti-

nal obstruction, irritation of the solar plexus by the pedicle of the cyst, adhesions, and peritonitis due to rupture of the cyst.

Lahey and Eckerson [14] have emphasized that the most important group of true retroperitoneal cysts is composed of the Wolffian cysts, arising from persistent remnants of any part of the early urogenital system. Other true retroperitoneal cysts are the lymphatic or chylous cysts, arising from obstructive phenomena and lined by fibrous tissue, and the mesocolic cysts, arising from pockets of peritoneum left between the opposed serous surfaces of the mesentery and parietal peritoneum in the early rotation of the colon from the left to the right. To complete the classification of true retroperitoneal cysts, Lahey and

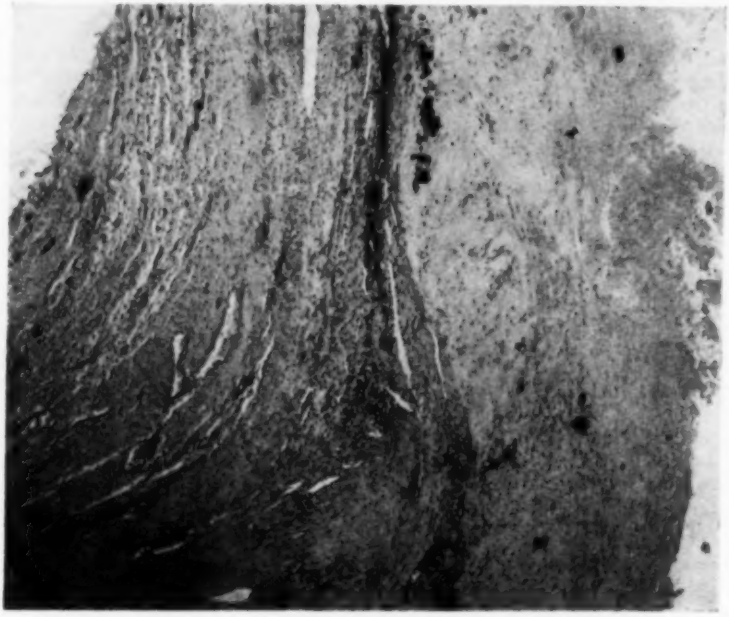

FIG. 6. Photomicrograph of the cyst wall. The arterial wall is on the left and the mural thrombus is on the right. The dense areas are calcium.

Eckerson have included dermoid cysts, parasitic and inflammatory cysts, and traumatic blood cysts. The history of an abdominal mass present for a five-year period, findings during marsupialization, and the pathologic diagnosis would tend to eliminate Wolffian, lymphatic or chylous, mesocolic, and dermoid cysts as the etiology of the retroperitoneal cyst in this case reported. The clinical course and normal white count, and a history of no abdominal trauma, would make a traumatic blood cyst and an inflammatory cyst unlikely. However, a parasitic cyst such as an echinococcus cyst can not be entirely excluded.

Kampmeier [15] has pointed out that pancreatic cysts may simulate abdominal aneurysms with both conditions representing a tumor. The cyst may or may

not present a transmitted pulsation which displaces the cyst laterally with each systole. Both lesions may have calcified walls, and pancreatic cysts may sustain bleeding and hematoma with organization. It is unlikely that this unusual retroperitoneal cyst was of pancreatic origin because of its location, displacing the liver to the left nearly across the midline and occupying the normal position of the liver. Also, the cystic fluid removed during marsupialization contained only a trace of amylase, and the pathologic diagnosis of the cyst wall and contents was interpreted as a saccular aneurysm or a hematoma which developed in a dissecting aneurysm.

MacNamara, Baker and Costich [11] point out that syphilis is seldom the cause of aneurysm of the hepatic artery. Pearlman [12] emphasizes that abdominal aortic aneurysm may exist for many years and remain relatively asymptomatic. In his case arteriosclerosis was probably the cause. Malloy and Jason [10] found that arteriosclerosis was the second most common cause of aneurysm of the hepatic artery, and while those within the substance of the liver were usually true aneurysms, false aneurysms or hematomas were most commonly retroperitoneal.

There was no history of trauma, and no clinical or serological evidence of lues in this case. There was, however, generalized arteriosclerosis and roentgen-ray evidence of calcification of the abdominal aorta. It would appear probable that this unusual retroperitoneal cyst was a saccular aneurysm or an encapsulated hematoma in a dissecting aneurysm, the most likely etiology being arteriosclerosis.

Summary

1. An unusual case of upper abdominal retroperitoneal cyst simulating a calcified hepatic cyst is reported.

2. In this case a positive Ferris-Blankenhorn sign was not of differential value.

3. The most likely etiology of this retroperitoneal cyst, based on the pathologic diagnosis is a saccular aneurysm or an encapsulated hematoma which had developed in a dissecting aneurysm. A pancreatic cyst, however, with hemorrhage or a large retroperitoneal hematoma from any cause, cannot be entirely excluded.

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EDITORIAL

THROMBOTIC THROMBOCYTOPENIC PURPURA

FULMINATING purpura hemorrhagica with profuse bleeding often presents an extremely difficult problem both as to diagnosis and treatment. Much remains to be learned about the hemorrhagic diseases, and the recent differentiation of a new clear-cut clinical and pathologic entity among the cases of "idiopathic" thrombocytopenic purpura marks a welcome advance in our knowledge of these conditions.

The first adequate report of the pathologic lesions in this disease is credited to Moschcowitz,[1] who described multiple hyaline thrombi in the terminal arterioles and capillaries, widely disseminated but most abundant in the myocardium. This was in a girl of 16 who died after a two weeks' illness characterized by fever, progressive, severe anemia and terminal neurologic disturbances. (The clinical description is inadequate.)

In 1936 Baer et al.[2] reported in detail four cases in which identical lesions were observed. Largely by exclusion they concluded that the thrombi were composed purely of blood platelets. At present about 25 cases have been reported in the American literature, in only two of which was the diagnosis made or strongly suspected ante mortem.[3, 4]

A majority of the reported cases have been young adult white females, but the disease has been observed in white males and in colored of both sexes. The onset of outspoken symptoms is usually fairly abrupt, occasionally fulminant, with malaise, weakness, fever, and often symptoms of an infection of the upper respiratory passages. Frequently there has been abdominal pain, anorexia, or nausea and vomiting. Frequently the acute symptoms have been preceded by a period of vague ill health,[2, 6, 8] or the syndrome has developed in a patient with some chronic disease, such as arthritis,[5] tuberculous enteritis,[6] or glomerulonephritis.[6, 7] Anemia may be obvious at the onset, or it develops under observation, often with great rapidity, and it usually becomes severe. It is independent of bleeding and often antedates the bleeding.

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It is not appreciably benefited by transfusions. There is often some degree of visible jaundice, or a café-au-lait tint in the skin.

Hemorrhagic manifestations invariably appear, although they vary in severity and are not always notable at the onset. There are usually numerous petechiae in the skin and visible mucous membranes, and often retinal hemorrhages. Microscopic hematuria is practically always present, and gross hematuria, oozing from the gums, hematemesis or melena may occur. In this respect these cases in the later stages may be clinically indistinguishable from fulminating cases of ordinary idiopathic thrombocytopenic purpura.

The most distinctive clinical feature is the appearance, usually late in the disease, of bizarre fluctuating neurologic disturbances of almost any conceivable type. There may be headache, dizziness, delirium, confusion, and drowsiness progressing to coma. Convulsions and Cheyne-Stokes respiration have been described in a number of cases. Pareses or paralyses suggesting disseminated focal injury of the brain are very common. These include aphasia, apraxia, deafness, facial paralysis, weakness or spasticity of one or more extremities, or hemiplegia. The outstanding characteristic of these disturbances is their extreme variability both in distribution and severity. They wax and wane in unpredictable fashion, and while one group of symptoms is subsiding new manifestations of injury elsewhere may appear. The cerebrospinal fluid (when examined) has been normal except in one case in which bleeding into the meninges had occurred. Massive intracerebral hemorrhage, such as occurs occasionally in ordinary idiopathic thrombocytopenic purpura, has not been reported. The neurologic disturbances and lesions observed in Fitzgerald's [8] cases have been described in detail by Adams et al.[9]

The course of the disease has been rapidly progressive, the duration after the appearance of outspoken symptoms varying from one week to two months, usually two to four weeks. In one case [3] there was a partial remission of one month. Milder types of the disease, if they occur, have not been recognized.

The blood shows the typical manifestations of a hemolytic anemia, although the severity of the anemia and the rate of hemolysis have varied greatly. In most cases the red cell count has fallen to two million or less, but the severity of the anemia may have been affected to some extent by the transfusions which were almost invariably administered. The anemia is normocytic and normochromic. Anisocytosis has not been marked. Spherocytosis has been described in two cases,[4, 7] but in these it was inconstant or variable. The reticulocytes are increased, in some cases markedly, and in the advanced stages normoblasts may appear in considerable numbers. The icterus index and serum bilirubin (retention type) are increased. The bone marrow shows a marked degree of erythroid hyperplasia.

[8] Fitzgerald, P. J., Auerbach, O., and Frame, E.: Thrombocytic acroangiothrombosis (platelet thrombosis of the capillaries, arterioles and venules), Blood **2**: 519–541, 1947.

[9] Adams, R. D., et al.: The neuropathological aspects of thrombocytic acroangiothrombosis. A clinico-anatomical study of generalized platelet thrombosis, J. Neurol., Neurosurg. and Psychiat. **11**: 27, 1948.

The leukocytes are normal or moderately increased in number. There is usually a moderate "shift to the left" of the neutrophiles, and in the advanced stages there may be a well marked leukemoid reaction. There is no eosinophilia in the blood or marrow.

There is a progressive diminution in platelets which are virtually absent in the advanced stages. With this there are the usual hemorrhagic phenomena associated with severe thrombocytopenia—a prolonged bleeding time and deficient clot-retraction with little alteration of the coagulation or prothrombin time. The tourniquet test has given variable results. It is generally agreed that the platelets are mechanically removed from the circulation by agglomeration in the innumerable thrombi formed in the peripheral vessels. There is no evidence of disturbed splenic function. The megakaryocytes in the bone marrow have been normal or increased in number, and when suitable material has been adequately studied,[3, 4, 6, 10] have shown no evidence of an arrest of platelet formation. In several cases many megakaryocytes were also present in the pulmonary capillaries, but not in all cases in which a search for them was made.

The mechanism of the hemolytic reaction has been studied adequately in only one case.[4] The agent apparently acts as strongly on normal transfused red cells as on those of the patient. It, therefore, probably does not depend upon an inherent defect in the cells, although their mechanical fragility was increased. There was a variable increase in osmotic fragility, but normal resistance to lysolecithin and heat (acid). Coomb's agglutination test for a specific antibody (globulin) was negative. If adequately confirmed, these tests would help greatly in differentiating this disease from the more common types of hemolytic anemia with which it might be confused. At present an unquestionable diagnosis can be established only by demonstrating the characteristic lesions in the vessels. The practicability of accomplishing this by biopsy has not been shown. There is a surprising lack of information regarding the occurrence of the lesions in the skin and skeletal muscles. Gore [6] has observed them in the skin and diaphragm. They are often present in the bone marrow and should be demonstrable in biopsied material, at least in some cases. It seems questionable, however, whether they are present with sufficient regularity and in sufficient number to make their demonstration in material obtainable with a trochar, a practicable and dependable procedure.

The thrombi, it is now clear, are composed (substantially) exclusively of platelets. Insignificant amounts of fibrin may be demonstrable. They are limited to the terminal arterioles and capillaries, to a much less extent (or not at all [6]) to the venules, and are never in the larger vessels. They are most numerous in the myocardium, renal cortex, adrenals and pancreas, frequent in the brain (when examined), and less constant or often in smaller numbers in many other organs, including the bone marrow, spleen, liver (portal spaces), gastrointestinal mucosa, thyroid, lung, trachea, lymph nodes, and

[10] Green, M. A., and Rosenthal, S.: Generalized platelet thrombosis. Report of three cases with necropsy findings, J. Mount Sinai Hosp. **16**: 110–120, 1949.

diaphragm. Great numbers of vessels may be involved, but never all of them, so that ischemic necroses are rare except small focal necroses in the myocardium and occasionally in the brain. The persistence of some patent vessels explains the variability and transient nature of the neurologic disturbances.

There has been difference of opinion as to whether the primary disturbance was an agglomeration of circulating platelets and secondary plugging of the capillaries, or an endothelial lesion with secondary accumulation of platelets at this site. The evidence now strongly favors the latter view, particularly the recent careful studies of Gore.[6] He found rare focal "prethrombotic lesions" in which there was a localized accumulation of hyaline material just beneath the endothelium. This thickens and bulges into the lumen, carrying with it at first a layer of intact endothelium which later breaks and furnishes a denuded area on which platelets accumulate, starting the thrombus. The latter is propagated for some distance within the vessels, but as a rule it remains free from the (usually) normal appearing endothelium except at the point of origin. The original hyaline material seems to be rapidly absorbed. The endothelium around the lesion proliferates actively, growing out over and covering the thrombus completely, and later often invading it. Late lesions may show varying degrees of organization. The occurrence of lesions in various stages of development indicates that the process is a continuing or repetitive one.

Perhaps the most characteristic feature of the lesions is the virtual absence of any inflammatory reaction in the walls of the vessels and adjacent tissues They are entirely different from those of periarteritis nodosa, disseminated lupus erythematosus, and of the usual infectious diseases. They resemble somewhat the lesions described by Allen and Spitz in scrub typhus.

Nothing definite is known as to the etiology of the disease. Blood cultures and other procedures have not revealed any infection of primary significance. An allergic origin has been suggested, partly because of the superficial resemblance of the lesions to those seen in the Shwartzman reaction. Hypersensitiveness to iodine [11] and to sulfonamides [5, 8] and urticaria have been reported, but this is exceptional.

Treatment thus far has been futile. Transfusions are of little if any benefit, even temporarily. Splenectomy, carried out in four cases (three nearly moribund),[2, 3, 7, 10] was ineffective. It would probably be justifiable to try this, as a frank experiment, in a few more cases in earlier stages of the disease, although the prospect that splenectomy will be curative now seems poor. Aureomycin was ineffective in one case so treated.[4]

The disease is rare but is probably commoner than has been supposed. It has probably most often been confused with ordinary idiopathic thrombocytopenic purpura, occasionally with other forms of hemolytic anemia. A clinical diagnosis should be possible in many cases if the observer is aware of

[11] Erich, W. E., and Sifter, J.: Thrombotic thrombocytopenic purpura caused by iodine, Arch. Path. 47: 447–449, 1949.

the condition. It should be strongly suspected in an acutely ill patient who shows both a thrombocytopenic purpura and a hemolytic anemia with retention jaundice. The diagnosis becomes highly probable if the transitory bizarre neurologic disturbances are also present. Further observations may show that the diagnosis can be established by biopsy, or possibly by a critical study of the hemolytic mechanism. Recognition is important to make possible adequate antemortem studies, as well as an accurate prognosis. It may also avert a useless splenectomy unless further study should establish the value of this procedure.

P. W. C.

REVIEWS

Proceedings of the First Clinical ACTH Conference. By JOHN R. MOTE, M.D., Editor. 607 pages; 23.5 × 15.5 cm. 1950. The Blakiston Company, Philadelphia. Price, $5.50.

This volume represents the Proceedings of the First ACTH Conference held in Chicago in October, 1949, under the auspices of the Armour Laboratories. During the preceding three years ACTH had been made available to a large number of investigators who studied the results of adrenal cortical stimulation in a wide variety of diseases. The Conference brought together all those engaged in this research so that each might profit by this opportunity to learn the results obtained by others working other areas of this virgin field.

In two days, 52 papers of 10 minute lengths were presented and discussed. Much of the data was of course of a preliminary and tentative character. Transcriptions of both the presentations and the discussions were made and after somewhat hurried editing the whole has been printed in this volume of 607 pages.

In a short summary of the Conference Dr. Mote points out that the bulk of the work consists of the studies of the metabolic and clinical effects of ACTH on normal human beings and on those exhibiting various endocrine abnormalities. Practically all of these were subjected to one or another type of complete metabolic balance study. Naturally another large segment is made up of studies of rheumatoid arthritis and of other clinical syndromes grouped under the designation of collagen diseases. Early exploratory investigations are reported dealing with the effects of ACTH in various disease entities, falling roughly into the groups of malignancies, hypersensitivities, infections, demyelinating diseases, diseases of muscle, and miscellaneous. It might be said that even by the date of the Conference ACTH had been tried in most of the clinical conditions for which there had previously been no effective therapy.

The general impression gained from the Conference is a confirmation of the extraordinary potency of ACTH and of the revolutionary effects these investigations and those dealing with cortisone have brought about in our concepts of pathogenesis. It is clear also that the clinical use of ACTH is not without dangers, and that such therapy should be undertaken only by those well acquainted with the field of metabolism and endocrinology and under conditions which facilitate adequate control.

This compilation presents the status of ACTH studies up to the fall of 1949. It is of course indispensable to all investigations in the biological sciences. The volume should, however, have a much wider distribution than this. The present greater availability of ACTH inevitably results in pressure on the internist to employ it in the treatment of patients. It is not too much to say that the internist must now acquaint himself with the basic data and methods in this new field just as the practicing clinician of 60 years ago had to study bacteriology.

The medical profession owes a debt of gratitude to the Armour Laboratories for having called the Conference and for making its proceedings generally available.

M. C. P.

The Cytologic Diagnosis of Cancer. By the Staff of the Vincent Memorial Laboratory of the Vincent Memorial Hospital, a gynecologic service affiliated with the Massachusetts General Hospital, Boston, Massachusetts; The Department of Gynecology, Harvard Medical School; published under the Sponsorship of The American Cancer Society. 229 pages with 153 figures; 16.5 × 25.5 cm. W. B. Saunders Company, Philadelphia. 1950. Price, $6.50.

This book is a laboratory manual which represents the experience of the authors in establishing the value of cytologic technics in the diagnosis of cancer.

In the various chapters, consideration is given to exfoliated cells of the female generative tract, the respiratory tract, the stomach, and the genito-urinary tract.

Two chapters are devoted to the cytology of serous fluids.

The technics used in obtaining the various secretions and methods employed in preparing smears for study are given in detail in the final chapter. The volume is well illustrated with low and high power photomicrographs and well executed drawings. All plates in the book are of uniform magnification. The illustrations cover noncancerous as well as malignant cells. This is most important from the standpoint of differentiation. A comprehensive bibliography is appended.

This volume should prove to be a most useful guide to those engaged in the broadening field of exfoliative cytology.

This book is not, nor is it intended to be, a substitute for experience.

H. R S.

A Primer of Venous Pressure. By GEORGE E. BURCH, M.D., Henderson Professor of Medicine, Tulane University School of Medicine, etc. 174 pages with 170 illustrations; 15.5 × 24 cm. Lea & Febiger, Philadelphia. 1950. Price, $4.00.

This is an extremely interesting discussion of the fundamentals of venous pressure. It provides an excellent physiological approach to this subject and presents much basic information. The book is well-written, and its value is increased by many diagrams, some of which appear more than once in this small text. The gaps in our knowledge of this subject are made apparent and one's interest in this field is stimulated. It is, therefore, regrettable that no bibliography is included. This volume is recommended to all physicians interested in the study of the circulation.

S. S.

Morbus Caeruleus: An Analysis of 114 Cases of Congenital Heart Disease with Cyanosis. Edited by E. MANNHEIMER, The Crown Princess Lovisa's Children's Hospital, Stockholm. 332 pages; 17.5 × 24.5 cm. Interscience Publishers, Inc., New York 3, N. Y. 1949. Price, $9.25.

This is a report of the results of various procedures used in the diagnosis of 114 cases of congenital cardiovascular malformations with cyanosis. The editor stresses the fact that this is not a textbook on congenital heart disease but an attempt to evaluate various clinical methods of studying these conditions, and to judge the results of the surgical treatment. Accordingly, there are detailed reports not only of the clinical and roentgenological findings but also of the more recently applied technics: angiocardiography, heart catheterization, and circulation time study. There is a well-written section on the embryology of the heart.

This book is an excellent example of the application of modern comprehensive methods to the diagnosis of congenital heart disease. It should be of interest to the cardiologist with some experience in this field. It was not intended, nor will it suffice as an independent text on this subject.

S. S.

Bridges' Dietetics For The Clinician. 5th Ed. Edited by HARRY J. JOHNSON, M.D., F.A.C.P. 898 pages; 16 × 24 cm. Lea & Febiger, Philadelphia. 1949. Price, $12.00.

The appearance of the fifth edition amply attests the popularity of this volume. The first three editions were planned directly by Dr. Bridges, whereas the fourth edition appeared posthumously. Now comes the fifth edition, thoroughly revised and edited by Dr. Johnson, who was associated in practice with Dr. Bridges, during the

time the first three editions were prepared. The material continues to be well organized and simply written, and the revision is adequate.

The list of contributing specialists has been increased and the material has been limited to that which the general practitioner of medicine, as well as the specialist, will find helpful in treating the patient. The material pertaining to the mechanics, physiology and chemistry of digestion has been markedly condensed and shorn of extraneous, non-practical discussion. The alphabetical arrangement of the various disease entities is a convenience. Each disease is first the subject of a brief general discussion, after which there follows one or more typical menus. The various food tables are most comprehensive and well arranged, and the table of contents or the index makes it easy to locate any desired topic.

The book has not only lived up to its previous high standard, but has stood the test of time, by careful revision, without an increase in its size. The present edition represents 898 pages as compared with 960 for the fourth and 1055 for the third edition. Perhaps the factual statement that the more one uses the volume, the more it seems to contain, is an indication of its value.

S. M.

BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Causes of Blindness in England and Wales. Medical Research Council Memorandum No. 24. By ARNOLD SORSBY. 42 pages; 24.5 × 15 cm. (paper-bound). 1950. H. M. Stationery Office, London. Price, 1s. 6d. net.

Clinical Electrocardiography. By FRANCIS F. ROSENBAUM, M.D., Assistant Clinical Professor of Medicine, Marquette University School of Medicine, etc.; edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), M.A.C.P., Hon. F.R.C.P. (Can.) D.S.M. (A.M.A.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University, etc. 153 pages; 24 × 16 cm. (reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work). 1950. Oxford University Press, New York. Price, $4.50.

Form- und Wachtstumsgesetze Drüsenbildender Karzinome. By PROF. DR. RICHARD BÖHMIG. 105 pages; 24.5 × 17 cm. (paper-bound). 1950. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, $3.35.

Gastritis Ulkus und Karzinom. By PROF. DR. J. BÜCKER. 89 pages; 24.5 × 17 cm. (paper-bound). 1950. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, $2.75.

Die Gewebsmastzellen im Menschlichen Knochenmark. By DR. MED. P. BREMY, Zürich. 78 pages; 21 × 14.5 cm. (paper-bound). 1950. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, $1.70.

Handbook of Medical Protozoology for Medical Men, Parasitologists and Zoologists. By CECIL A. HOARE, D.Sc. (Lond.), Protozoologist to the Wellcome Laboratories of Tropical Medicine, London. 334 pages; 23.5 × 15.5 cm. 1950. The Williams & Wilkins Company, Baltimore. Price, $7.00.

Human Milk: Wartime Studies of Certain Vitamins and Other Constituents. Medical Research Council Special Report Series No. 269. By S. K. KON and E. H. MAWSON. 188 pages; 24.5 × 15 cm. (paper-bound). 1950. His Majesty's Stationery Office, London. Price, 4 shillings net.

Human Sterilization: Techniques of Permanent Conception Control. By ROBERT LATOU DICKINSON, M.D., and CLARENCE JAMES GAMBLE, M.D. 39 pages; 25.5 × 17.5 cm. 1950.

Lectures on Medicine to Nurses. By A. E. CLARK-KENNEDY, M.D., F.R.C.P., Fellow of Corpus Christi College, Cambridge, etc.; with a Foreword by MISS CLARE ALEXANDER, Matron of the London Hospital. 288 pages; 22 × 14.5 cm. 1950. The Williams and Wilkins Company, Baltimore. Price, $3.50.

Management of Peripheral Arterial Diseases. By SAUL S. SAMUELS, A. M., M.D., Chief of the Department of Arterial Diseases, Stuyvesant Polyclinic Hospital, New York, etc. 345 pages; 22.5 × 14.5 cm. 1950. Oxford University Press, New York. Price, $7.50.

Manual of Rheumatic Diseases. By W. PAUL HOLBROOK, M.D., and DONALD F. HILL, M.D., Tucson, Arizona; with the assistance of CHARLES A. L. STEPHENS, JR., M.D. 182 pages; 21 × 14.5 cm. 1950. The Year Book Publishers, Inc., Chicago. Price, $4.25.

The Mask of Sanity: An Attempt to Clarify Some Issues About the So-Called Psychopathic Personality. 2nd ed. By HERVEY CLECKLEY, M.D., Professor of Psychiatry and Neurology, University of Georgia School of Medicine. 569 pages; 22.5 × 14.5 cm. 1950. The C. V. Mosby Company, Saint Louis. Price, $6.50.

Onderzoek Naar Het Effect Van Enkele Sympathicusremmende Stoffen Bij Patienten Met Maag- of Duodenumzweren. By JAN FREDERIK VISSER. 140 pages; 24.5 × 16 cm. (paper-bound). 1950. Drukkerij Trio, Hillegersberg.

The Pathology of Internal Diseases. 5th ed. By WILLIAM BOYD, M.D., Dipl. Psych., M.R.C.P. (Edin.), F.R.C.P. (Lond.), F.R.C.S. (Canada), LL.D. (Sask.), D.Sc. (Man.), M.D. (Oslo), F.R.S. (Canada), Professor of Pathology and Bacteriology in the University of Toronto, Toronto. 866 pages; 24 × 16 cm. 1950. Lea & Febiger, Philadelphia. Price, $11.00.

Praktische Elektrokardiographie. By FRANZ KIENLE. 448 pages; 26.5 × 18 cm. 1950. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 38.–

Principles of Internal Medicine. T. R. HARRISON, Editor-in-Chief; Editors: PAUL B. BEESON, WILLIAM H. RESNIK, GEORGE W. THORN, M. M. WINTROBE. 1216 pages; 26 × 18 cm. (paper-bound, pre-publication copy). 1950. The Blakiston Company, Philadelphia.

Recopilacion de Leyes, Reglamentaciones, Decretos y Resoluciones—Tomo III—Julio 1946 a Diciembre 1947. 984 pages; 27 × 18.5 cm. (paper-bound). 1948. Secretaria de Salud Publica de la Nacion, Republica Argentina.

Researches on the Measurement of Human Performance. Medical Research Council Special Report Series No. 268. By N. H. MACKWORTH. 156 pages; 24.5 × 15 cm. (paper-bound). 1950. His Majesty's Stationery Office, London. Price, 4 shillings net.

CALENDAR OF A.C.P. REGIONAL MEETINGS

Region	City	Dates	Governor or Chairman	Official Guest(s) from Board of Regents
North Dakota	Minot	September 9, 1950	Robert B. Radl, Governor Paul J. Breslich, Local Chairman	LeRoy H. Sloan, Regent
Montana-Wyoming	Billings	September 15–16, 1950	Harold W. Gregg, Governor Wayne Gordon, Arrangements	William S. Middleton, President
Western Pennsylvania	Pittsburgh	September 27, 1950	Charles W. Morton, Governor	Maurice C. Pincoffs, President-Elect
Oklahoma-Arkansas	Tulsa	September 30, 1950	Wann Langston, Governor for Oklahoma A. A. Blair, Governor for Arkansas	Walter L. Palmer, Regent and Chairman, Board of Governors E. R. Loveland, Executive Secretary
Mississippi	Jackson	October 7, 1950	John G. Archer, Governor	William S. Middleton, President E. R. Loveland, Executive Secretary
Northern California	San Francisco	October 13, 1950	Dwight L. Wilbur, Governor	Maurice C. Pincoffs, President-Elect
Southern California	Los Angeles	October 14, 1950	Leland Hawkins, Governor	Maurice C. Pincoffs, President-Elect
Western New York	Rochester	October 14, 1950	Edward C. Reifenstein, Governor William S. McCann, General Chairman	William S. Middleton, President E. R. Loveland, Executive Secretary
Arizona	Tucson	October 14, 1950	Leslie R. Kober, Governor	LeRoy H. Sloan, Regent
Pacific Northwest (Oregon, Washington, Idaho, Alberta, and British Columbia)	Portland	October 27–28, 1950	Howard P. Lewis, Governor for Oregon George H. Anderson, Governor for Washington Samuel M. Poindexter, Governor for Idaho John W. Scott, Governor for Alberta and British Columbia	Cyrus C. Sturgis, Regent
New Jersey	Trenton	November 1, 1950	Edward C. Klein, Jr., Governor	William S. Middleton, President E. R. Loveland, Executive Secretary
Puerto Rico	San Juan	November 5, 1950	Rafael Rodriguez-Molina, Governor	Maurice C. Pincoffs, President-Elect

CALENDAR OF A.C.P. REGIONAL MEETINGS—*Continued*

Region	City	Dates	Governor or Chairman	Official Guest(s) from Board of Regents
Utah	Salt Lake City	November 11, 1950	Fuller B. Bailey, Govenor	Walter L. Palmer, Regent and Chairman, Board of Governors
Midwest (Illinois, Indiana, Iowa, Michigan, Minnesota, Ohio, and Wisconsin)	Madison	November 18, 1950	Karver L. Puestow, Governor for Wisconsin, General Chairman Walter L. Palmer, Governor for Northern Illinois Charles H. Drenckhahn, Governor for Southern Illinois James O. Ritchey, Governor for Indiana Benjamin F. Wolverton, Governor for Iowa Douglas Donald, Governor for Michigan Wesley W. Spink, Governor for Minnesota Charles A. Doan, Governor for Ohio	William S. Middleton, President LeRoy H. Sloan, Regent George Morris Piersol, Secretary-General E. R. Loveland, Executive Secretary
Kentucky	Lexington	December 9, 1950	J. Murray Kinsman, Governor	(Pending)
Midsouth (Louisiana, Tennessee, and Texas)	Memphis	January 12–13, 1951	William C. Chaney, Governor for Tennessee, General Chairman Thomas Findley, Governor for Louisiana David W. Carter, Jr., Governor for Texas	(Pending)
Southeastern (Alabama, Florida, Georgia, and South Carolina)	Charleston	January 26–27, 1951	Robert Wilson, Jr., Governor for South Carolina, General Chairman E. Dice Lineberry, Governor for Alabama William C. Blake, Governor for Florida Carter Smith, Governor for Georgia	William S. Middleton, President E. R. Loveland, Executive Secretary
Colorado	Denver	February 20, 1951	Ward Darley, Governor	(Pending)
Nebraska	Omaha	February ?, 1951	Joseph D. McCarthy, Governor	(Pending)
Kansas	Wichita	March 16, 1951	William C. Menninger, Governor	William S. Middleton, President
North Carolina	Chapel Hill	(Pending)	Elbert L. Persons, Governor	(Pending)

COLLEGE NEWS NOTES

OKLAHOMA–ARKANSAS REGIONAL MEETING

Mayo Hotel, Tulsa, Okla.

Saturday, September 30, 1950

WANN LANGSTON, M.D., F.A.C.P., *Governor for Oklahoma*

A. A. BLAIR, M.D., F.A.C.P., *Governor for Arkansas*

PROGRAM

MORNING SESSION

9:00 Registration.

9:45 Welcome.

Presiding Officer

EMRY G. HYATT, M.D., F.A.C.P., Tulsa

10:00 Recent Advances in the Diagnosis and Treatment of Cerebral Vascular Disease.
R. E. CARPENTER, M.D. (Associate), Oklahoma City, Okla.

10:15 Relationship of Vitamins to Disease.
PAUL DAY (by invitation), Professor of Chemistry, University of Arkansas, Little Rock, Ark.

10:30 Anterior Pituitary Insufficiency.
PAUL STRONG, M.D. (Associate), Tulsa, Okla.

10:45 Pulmonary Emphysema; A Diagnostic and Therapeutic Problem.
JOHN J. DONNELL, M.D. (Associate), Oklahoma City, Okla.

11:00 What's New in Medicine.
HOWARD C. COGGESHALL, M.D., F.A.C.P., Dallas, Tex., and ARTHUR A. HELLBAUM, M.D. (by invitation), Professor of Pharmacology, University of Oklahoma School of Medicine.

11:45 Intermission.

12:00 Panel: Gastro-Intestinal Diseases.
WANN LANGSTON, M.D., F.A.C.P., Oklahoma City, Okla., *Moderator.*
WALTER L. PALMER, M.D., F.A.C.P., Chicago, Ill.
JEROME S. LEVY, M.D., F.A.C.P., Little Rock, Ark.
S. C. SHEPARD, M.D., F.A.C.P., Tulsa, Okla.
HARRY A. DANIELS, M.D., F.A.C.P., Oklahoma City, Okla.

1:00 Luncheon.

AFTERNOON SESSION

Presiding Officer

A. A. BLAIR, M.D., F.A.C.P., Fort Smith, Arkansas, *Governor for Arkansas*

2:00 Steroids other than ACTH and Cortisone in the Treatment of Rheumatoid Arthritis.
RALPH PATTERSON (by invitation), Colonel (MC), U. S. Army, Army and Navy Hospital, Hot Springs, Ark.

2:15 Diseases of the Esophagus.
BERT E. MULVEY, M.D., F.A.C.P., Oklahoma City, Okla.

2:30 Pulmonary Silicosis.
H. A. Brocksmith, M.D. (by invitation), Medical Consultant, Muskogee Veterans Administration Hospital, Muskogee, Okla.
2:45 Rôle of Potassium in the Body.
John B. Morey, M.D., F.A.C.P., Ada, Okla.
3:00 Address.
Walter L. Palmer, M.D., F.A.C.P., Chicago, Ill.
3:30 Intermission.
3:45 Modern Concepts of Hepatitis in Cirrhosis.
Alfred Kahn, M.D. (Associate), Little Rock, Ark.
4:00 Clinical Pathological Conference.
Leo Lowbeer, M.D. (by invitation), Pathologist, Hill Crest Hospital, Tulsa, Okla., and
Robert H. Bayley, M.D., F.A.C.P., Professor of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Okla.

Evening Session

(For Fellows, Associates, Invited Guests and Their Wives)

Mayo Hotel

7:00 Social Hour.
8:00 Dinner (Informal).
Guest Speakers:
Mr. E. R. Loveland, Executive Secretary, American College of Physicians, Philadelphia, Pa.
Dr. Walter L. Palmer, F.A.C.P., Chairman, Board of Governors, American College of Physicians, Chicago, Ill.

MISSISSIPPI REGIONAL MEETING

Heidelberg Hotel, Jackson, Miss.

Saturday, October 7, 1950

John G. Archer, M.D., F.A.C.P., Governor for Mississippi, *Presiding*

Afternoon

1:00 Registration.
1:30 The Development of a Rural Medical Service—What Mississippi Is Doing About It.
Felix Underwood, M.D., F.A.C.P., Executive Officer, Mississippi State Board of Health, Jackson, Miss.
2:00 Aging in the Willis' Circle.
C. M. Mezey, M.D. (by invitation), Pathologist, Veterans Administration Hospital, Gulfport, Miss.
2:30 The Non-Arteriosclerotic Nervous Diseases of Old Age.
Philip Work, M.D., F.A.C.P., Long Beach, Miss.
3:00 Headache.
Lyle Motley, M.D., F.A.C.P., Assistant Professor of Medicine, University of Tennessee, Memphis, Tenn.
3:30 Intermission.

3:45 Experience with and Treatment of an Unusual Case of Enterococcal Endocarditis.
JOHN T. LANE, M.D. (Associate), Chief of Medical Service, Veterans Administration Hospital, Biloxi, Miss.

4:15 The Treatment of Chronic Ulcerative Colitis by Diet.
PHILIP H. JONES, M.D., F.A.C.P., Professor of Clinical Medicine, Tulane University, New Orleans, La.

4:45 A Discussion of Some of Our Current Problems in Nutrition.
ROBERT E. STONE, M.D., F.A.C.P., Associate Director, Nutrition Clinic, Hillman Hospital, Birmingham, Ala.

EVENING

6:00 Social Hour (Silver Room).

7:00 Banquet (Rose Room). Informal.
Address by the Guest of Honor:
"The Open Mind in Medicine."
WILLIAM S. MIDDLETON, M.D., F.A.C.P., President of the American College of Physicians; Dean of the University of Wisconsin Medical School, Madison, Wis.

WESTERN NEW YORK REGIONAL MEETING

Rochester Academy of Medicine

1441 East Avenue, Rochester, N. Y.

Saturday, October 14, 1950

EDWARD C. REIFENSTEIN, M.D., F.A.C.P., Governor for Western New York

PROGRAM

MORNING SESSION

9:15 Registration.

Scientific Program

WILLIAM S. MCCANN, M.D., F.A.C.P., Rochester, N. Y., *Presiding*

9:30 Chronic Ulcerative Colitis with Pyodermia Gangrenosa of the Leg; Results of Treatment with Combined Antibiotics: Case Report.
JAMES F. CONNER, M.D. (Associate), Rochester, N. Y.

9:40 Myocardial Infarction after Penicillin—Probable Sensitization Reaction: Case Report.
MORRIS E. MISSAL, M.D., F.A.C.P., Rochester, N. Y.

9:50 Porphyrinuria in Periarteritis Nodosa: Case Report.
RICHARD F. PLATZER, M.D. (Associate), Clifton Springs, N. Y.

10:00 Clinical Ballistocardiography.
HERBERT R. BROWN, JR., M.D. (Associate), Rochester, N. Y.

10:20 Cardiac Cirrhosis.
CORBET S. JOHNSON, M.D. (Associate), Waverly, N. Y.

10:30 Determination of Rheumatic Activity in Arthritis by Turbidometric Assay of Serum with a Quaternary Ammonium Compound, Octab.
RALPH F. JACOX, M.D. (Associate), Rochester, N. Y.

10:50 Study of Muscle Lesions and Rheumatic Nodules in Patients Receiving Cortisone Therapy.
BERNARD M. NORCROSS, M.D. (Associate), L. MAXWELL LOCKIE, M.D., F.A.C.P., and JOHN H. TALBOTT, M.D., F.A.C.P., Buffalo, N. Y.

11:10 Giant Follicular Lymphoblastoma: Case Report.
SAMUEL E. COHEN, M.D., F.A.C.P., Elmira, N. Y., and CORBET S. JOHNSON, M.D. (Associate), Waverly, N. Y.

11:20 Hemolytic Mechanisms in Hereditary Spherocytosis.
LAWRENCE E. YOUNG, M.D., F.A.C.P., Rochester, N. Y., and RICHARD F. PLATZER, M.D. (Associate), Clifton Springs, N. Y.

11:40 Discussion.
WILLIAM S. MIDDLETON, M.D., F.A.C.P., President, American College of Physicians, Madison, Wis.

Luncheon Rochester Academy of Medicine.

AFTERNOON SESSION

EDWARD C. REIFENSTEIN, M.D., F.A.C.P., Syracuse, N. Y., *Presiding*

2:00 Pulmonary Calcification and Histoplasmin Sensitivity in New York State.
G. W. CRONK, M.D. (Associate), Syracuse, N. Y.

2:20 Appraisal of Strict Bed Rest in Tuberculosis following Thoracoplasty.
HARRY A. BRAY, M.D., F.A.C.P., Ray Brook, N. Y.

2:40 Steroid Hormones in the Treatment of Rheumatic Disease.
CHARLES L. STEINBERG, M.D., F.A.C.P., Rochester, N. Y.

3:00 Hemagglutination Test for Tuberculosis.
PAUL A. BUNN, M.D. (Associate), CHARLES ADAIR, M.D. (by invitation), and O. D. CHAPMAN, M.D., F.A.C.P., Syracuse, N. Y.

3:20 Pathogenesis of Ascites in Laennec's Cirrhosis.
WILLIAM W. FALLOON, M.D. (by invitation), Syracuse, N. Y.

3:40 Some Unusual X-Ray Problems Relative to the Chest and Cardiovascular System.
GEORGE H. RAMSAY, M.D. (by invitation), Rochester, N. Y.

4:00 Bacteroides Infections.
O. D. CHAPMAN, M.D., F.A.C.P., Syracuse, N. Y.

4:20 Discussion.
WILLIAM S. MIDDLETON, M.D., F.A.C.P., President, American College of Physicians, Madison, Wis.

4:40 Clinical-Pathological Conference.
RICHARD H. LYONS, M.D., F.A.C.P., Syracuse, N. Y.

EVENING

Rochester Club

6:30 Reception and Cocktails.

7:15 Dinner.

Toastmaster: CHRISTOPHER PARNALL, JR., M.D., F.A.C.P.

Brief Addresses:

WILLIAM S. MIDDLETON, M.D., F.A.C.P.
WILLIAM S. MCCANN, M.D., F.A.C.P.
EDWARD R. LOVELAND, Executive Secretary, A.C.P.
EDWARD C. REIFENSTEIN, M.D., F.A.C.P.

New Life Members

The College is gratified to announce that Dr. Martin DeForest Smith, New York, N. Y., and Dr. Albert Gordon Bower, Pasadena, Calif., have become Life Members of the American College of Physicians since the publication of the latest issue of this journal.

Postgraduate Course in Allergy

A Postgraduate Course in Allergy will be offered by the American Academy of Allergy on October 26, 27 and 28, 1950. The Course will be sponsored by McGill University and will be held in Montreal, Que., Canada.

University of Pennsylvania Postgraduate Course

The University of Pennsylvania Graduate School of Medicine announces a new course, "Current Advances in Medicine and Surgery." This course will be an excellent broad review of Medicine and Surgery during the past year and it is planned that the course will be given annually. The first session will be from Monday, September 25, through Friday, September 29, 1950. The tuition fee will be $100.00 for physicians in general; alumni of the Graduate School of Medicine are exempt and pay only a registration fee of $10.00. All fees are payable on application. Full information and application form may be obtained through the Office of the Dean, Graduate School of Medicine, University of Pennsylvania, Philadelphia 4, Pa.

Special Oral Examination, American Board of Internal Medicine

The American Board of Internal Medicine will conduct oral examinations, including those for the sub-specialties, October 26, 27 and 28, 1950, at Washington, D. C., and on December 7, 8 and 9, 1950, at New York. The closing date for acceptance of applications was announced as August 19, 1950. Candidates eligible this year cannot be admitted to oral examinations in 1951, unless illness interferes.

The American Association of Blood Banks will hold its third annual meeting October 12 to 14, 1950 at the Stevens Hotel, Chicago, Ill. Among the doctors scheduled to address the sessions are: Dr. Edwin T. Thorsness, F.A.C.P., Dubuque, Iowa; Dr. Warren B. Cooksey, F.A.C.P., Detroit, Mich.; Dr. Tibor J. Greenwalt, F.A.C.P., Milwaukee, Wis.; Dr. Alexander S. Wiener, F.A.C.P., Brooklyn, N. Y.; Capt. Lloyd R. Newhouser, (MC), U.S.N., F.A.C.P., Washington, D. C.; Dr. Philip Levine, F.A.C.P., Raritan, N. J.; Dr. Steven O. Schwartz, F.A.C.P., Chicago, Ill. and Dr. Quin B. DeMarsh (Associate), Seattle, Wash.

In addition to the papers to be presented there will be panel discussions and scientific and commercial exhibits.

The Cook County Graduate School of Medicine, connected with the Cook County Hospital of Chicago, gives many special courses for physicians in Chicago and vicinity. The courses generally are organized on the basis of one day a week and distributed over a period of some months. Courses are available in the Divisions of General Surgery, Internal Medicine, Otolaryngology, Pathology, Neurology, Pediatrics, and Gynecology and Obstetrics.

Those in the Division of Internal Medicine include: Heart Disease and Electrocardiography; Hematology; Technic of Physical Examination and Diagnosis of the

Chest; Cardiovascular Disease; Clinical Interpretation of X-Ray Findings; Allergy and Related Conditions; Medical and Surgical Diabetes; Gastroenterology; Physical Diagnosis; Medical Emergencies, Diagnosis and Treatment. Additionally, basic courses are given in the Biochemical Background of Clinical Medicine and in Pathology and Laboratory Medicine. The Directors of these courses in the field of Internal Medicine and Pathology are all Fellows of the American College of Physicians. Dr. Frederick Tice, F.A.C.P., is the Chairman of the Board of Trustees. Information concerning the courses is available through the Cook County Graduate School of Medicine, 427 South Honore Street, Chicago 12.

Honor to Dr. William J. Kerr

J. B. Lippincott Company has published a volume, "Contributions in Medicine," consisting of a number of papers published in a 60th birthday edition, in honor of William J. Kerr, M.D., F.A.C.P., Professor of Medicine at the University of California Medical School, San Francisco. The initial chapter is entitled, "The Career of William John Kerr to his Sixtieth Year," by Chauncey D. Leake, Executive Vice President of the University of Texas Medical School. The book is edited by Theodore L. Althausen, M.D., F.A.C.P., Henry D. Brainerd, M.D. (Associate), John B. Lagen, M.D., and Salvatore P. Lucia, M.D., and a volume has been contributed to the College Library.

Research Grants and Fellowships to Be Available in 1951 by the Life Insurance Medical Research Fund

Applications for 1951 grants in aid of research on cardiovascular problems will be received by the Life Insurance Medical Research Fund up to November 15, 1950. Support is available for physiological, biochemical, and other basic research which bears on cardiovascular problems, as well as for clinical investigation in this field. Preference is given to fundamental research. It is expected that about $550,000 will be awarded for these grants.

Applications for postdoctoral fellowships for training in research in 1951–52 will also be received by this Fund up to November 1, 1950. Preference is given to candidates who wish to work in the broad field of cardiovascular function or disease and to candidates who wish to work in institutions other than those in which they have obtained most of their experience. A doctor's degree (M.D. or Ph.D.), or the equivalent is required. The annual stipend varies, as a rule being between $3,000 and $4,000, with larger amounts in special cases. At least 15 postdoctoral fellowships will be available.

New grants and fellowships will become available on July 1, 1951.

A number of predoctoral fellowships for basic training in research will also be awarded. Details are available on request.

Further information and application blanks may be secured from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103d Street, New York 29, New York.

Captain Bartholomew W. Hogan, (MC), USN, F.A.C.P., recently assumed command of the U. S. Naval Medical School, National Naval Medical Center, Bethesda, Md.

Dr. Jacob C. Geiger, F.A.C.P., Director of Public Health, San Francisco, was honored on August 2 by the Foreign Minister of Spain through the Acting Consul

General of Spain, in San Francisco, who conferred on him the *Officer's Cross de la Orden del Merito Civil Catholica.* Dr. Geiger's citation stated that this honor was "For distinguished service in Public Health and Science, to Spanish people everywhere, especially in Central and South America."

Dr. Oswald F. Hedley, F.A.C.P., of the U. S. Public Health Service, who is serving as Chief of the Public Health Division, ECA Mission to Greece, returned recently to the United States to confer about the Greek health program. Dr. Hedley reported that the health of the Greek people reached its highest postwar level in 1949, and that the three most important problems are tuberculosis, lack of sanitation and a shortage of trained health workers, particularly nurses.

Dr. Thomas P. Murdock, F.A.C.P., Meriden, Conn., was unanimously elected to the Board of Trustees of the American Medical Association for a five year term at the Annual Session of the A.M.A., held in San Francisco in June. Dr. Murdock is also a member of the A.M.A. House of Delegates and the Judicial Council.

Dr. Francis F. Borzell, F.A.C.P., Philadelphia, Pa., was reëlected Speaker of the House of Delegates of the A.M.A. At the same time, Dr. James R. Reuling, F.A.C.P., Bayside, N. Y., was reëlected Vice Speaker of the House of Delegates.

Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., was elected Chairman of the Board of Trustees of the A.M.A. at the reorganization meeting of the Board.

Dr. Israel M. Rabinowitch, F.A.C.P., 1538 Sherbrooke St., W., Montreal 25, Que., Canada, has a complete set of the ANNALS OF INTERNAL MEDICINE, starting with Vol. 1, No. 1, 1927, and coming completely up to the present time, which he will sell for a reasonable price. Complete volumes of the ANNALS are now next to impossible to procure.

Captain Ray C. Lounsberry (MC), USNR, F.A.C.P., San Diego, Calif., is the first reserve officer in the Eleventh Naval District to be retired under the Navy Reserve plan which retires reserve officers who have had 20 years service and have reached the age of 60. This announcement will be interesting to others who have carried on their reserve activities in the Navy and who at last will be rewarded by being retired with retirement pay in keeping with their seniority, rank, period of service, etc.

Dr. H. Lee Quickel, F.A.C.P., Lt. Col., U. S. Army, Ret'd, now of Raleigh, N. C., has accepted a temporary appointment with the Division of Tuberculosis Control, North Carolina State Board of Health, where he will interpret 70 mm. chest films until an experienced physician can be obtained as a regular employee.

The New Jersey Gastroenterological Society, which is a Chapter of the National Gastroenterological Association, at its last meeting in June elected Dr. Sidney Rosenthal (Associate), Newark, N. J., as President; Dr. Andrew Klein, F.A.C.P., Newark, N.J., as Vice President, and Dr. Hyman I. Goldstein (Associate), Camden, N. J., as one of the representatives to the National Gastroenterological Association.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., recently delivered lectures at the William Beaumont General Hospital, El Paso, Tex., and at the U. S. Veterans Administration Hospital at Tuscaloosa, Ala.

Dr. James E. Paullin, M.A.C.P., Atlanta, was given a testimonial dinner by Emory University medical alumni on June 2, 1950. As a tribute to him, two projects were adopted by the alumni: (1) the James E. Paullin Scholarship Fund was established for the help of needy and worthy medical students at the University; (2) a portrait of Dr. Paullin is to be painted and placed in the University halls.

Dr. Paullin and Mrs. Paullin are convalescing from a serious automobile accident which occurred two days following the testimonial dinner.

Dr. Beeckman J. Delatour, F.A.C.P., heretofore Associate Professor of Medicine at New York University, has accepted an appointment as Clinical Director and Director of Medical Service at the American Hospital of Paris which has been restored following World War II. Dr. Delatour graduated from Johns Hopkins University School of Medicine in 1915 and did postgraduate work in Paris and other European countries. He has been a Fellow of the American College of Physicians since 1940.

The American Hospital of Paris, a million dollar plant, was completed in 1926 as a memorial to those who served in World War I. Its services are available to any American citizen requiring medical care. It has 153 beds and 20 bassinets and an outpatient service. The Advisory Board in America makes a limited number of appointments to residency and internship in the hospital.

Hugh Tatlock, M.D., F.A.C.P., Northampton, Mass., was recently appointed Consulting Internist to the Belchertown State School and Hospital.

Henry A. Tadgell, M.D., F.A.C.P., Belchertown, Mass., was recently elected President of the Hampshire District Medical Society (Massachusetts) for 1950–51.

OBITUARIES

DR. EDSON WILLIAM GLIDDEN

Dr. Edson William Glidden, F.A.C.P., who died April 26, 1950, of coronary occlusion, was a graduate of the Medical School of the University of Maryland, 1907. Following his internship at the University Hospital, Baltimore, he began his career in tuberculosis as a resident with Dr. David Lyman at Gaylord Farm Sanatorium in Connecticut. After a few years there he left to become Assistant Superintendent of the Maryland State Sanatorium, and after a few years accepted an appointment as Assistant Superintendent of the Lakeville State Sanatorium in Massachusetts, where he remained for seven years. He then returned to Gaylord Farm for two years.

At the beginning of the first World War he became a civilian tuberculosis expert for the War Risk Bureau, and after the Armistice, he was called to Georgia to rehabilitate the Georgia State Sanatorium. Here he did an outstanding job in reconstruction and rehabilitation of an old institution, together with reorganization of the medical service.

In 1931 he accepted the invitation of the Worcester County Commissioners to build and operate the Worcester County Sanatorium. This institution in West Boylston is one of the best planned and built sanatoria in the East. Dr. Glidden to an unusual extent combined abilities of the clinician with those of the administrator, and his work in Worcester County is well known in the field of tuberculosis.

Dr. Glidden had been a Fellow of the American College of Physicians since 1928.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts

DR. EVERETT KINNE GEER

Everett Kinne Geer, B.S., M.D., F.A.C.P., of St. Paul, Minn., died May 3, 1950, in an airplane crash. He was born in St. Paul, Minn., January 14, 1893, and received his B.S. degree from the University of Minnesota in 1915 and his M.D. degree from the same institution in 1917. He became a Fellow of the American College of Physicians in 1928.

Dr. Geer was a Diplomate of the American Board of Internal Medicine and had been Clinical Assistant Professor of Medicine at the University of Minnesota Medical School. He manifested a deep and wide interest in tuberculosis during all of his scientific life and made several contributions to medical literature, being especially interested in the control of tuberculosis among students of nursing. He was Chief of the Tuberculosis Department, Ancker Hospital, St. Paul; Chief Consultant in Tuberculosis, Veterans Administration District Office, Fort Snelling; Medical Director of the Children's Preventorium of Ramsey County; Consultant, Pokegama Sanatorium. Additionally, he served as a Staff Physician to several hospitals in St. Paul.

Dr. Geer was a Fellow of the American Medical Association, a member of the American Sanatorium Association, the American Trudeau Society and the National Tuberculosis Association. He was a past president of the Medical Forum of St. Paul and a former member of the Executive Committee of the Ramsey County Medical Society.

WESLEY W. SPINK, M.D., F.A.C.P.,
Governor for Minnesota

DR. FREDERICK GUSTAVUS BUESSER

Frederick Gustavus Buesser, M.D., F.A.C.P., was born in Troy, N. Y., April 27, 1881. He was a graduate of Wayne University College of Medicine, 1905. From 1906 until the time of his death, he was on the faculty of Wayne University College of Medicine, serving through the various ranks, starting with Clinical Assistant and terminating in Professor of Clinical Medicine. He was active on the Staffs of the Harper, City of Detroit Receiving and the Jennings Hospitals, and the Detroit Tuberculosis Sanatorium. During World War I, Dr. Buesser served overseas with the Medical Corps, U. S. Army, rising to the rank of Major. He did some special work on influenza and pneumonia in connection with his assignment at Base Hospital No. 17, where he served as Chief of Medicine during 1919.

Dr. Buesser was a Fellow and past President of the Detroit Academy of Medicine, a member of the Wayne County Medical Society, the Michigan State Medical Association and the American Medical Association. He was a Diplomate of the American Board of Internal Medicine and became a Fellow of the American College of Physicians on April 3, 1922.

During the 20th Annual Session of the College at Detroit in 1936, Dr. Buesser was Chairman of the Committee on Publicity and a member of the Executive Committee for the meeting.

He died July 1, 1950, after a long illness.

DR. JOHN M. MESMER

John M. Mesmer, M.D., F.A.C.P., died, June 12, 1950, in Buffalo, N. Y., after an illness of four months. He was born in Buffalo, September 19, 1875; graduated from the University of Buffalo School of Medicine in 1896 and pursued postgraduate work in internal medicine at the University of Vienna, 1898–99.

From 1900 to 1908, he was Associate in Medicine at the University of Buffalo School of Medicine; 1900–14, member of staffs, Sisters of Charity and the Erie County Hospitals; 1914–29, member of staff, Deaconess Hospital; 1924–28, Attending Physician, Buffalo City Hospital; 1926–39, Attending Physician, Millard Fillmore Hospital, and since 1940, Consultant at this institution. He was a Fellow of the American Medical Association, a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1931. He was associated with the late Dr. Henry Buswell in the practice of internal medicine until 1918.

Dr. Mesmer was an able clinician and an inspiring teacher and consultant. He never spared himself attending his patients or working with his colleagues. He always insisted upon thoroughness, and as a discussor, he frequently emphasized the importance of the art of medicine as well as the science of medicine. He is mourned by many professional and lay friends who will always remember his sincerity.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,
Governor for Western New York

DR. CHARLES HENRY GRAENING

Dr. Charles Henry Graening of Waverly, Iowa, was born in 1871 and received his medical training at the State University of Iowa College of Medicine, M.D., 1893. For many years he was Medical Director of the Lutheran Mutual Aid Society and was particularly interested in pediatrics and general medicine. He retired from active work in 1946.

Dr. Graening became an Associate of the American College of Physicians in 1926 by virtue of being a member of the American Congress on Internal Medicine from 1924, that society being merged with the College later. He died on May 13, 1950, at the age of 78 of heart disease.

DR. HOWARD COOMBS MILLER

Howard Coombs Miller, M.D., Youngstown, Ohio, died in the Southside unit of Youngstown Hospital, May 14, 1950, of multiple gastric ulcers; aged 73. Dr. Miller received his medical training at Western Reserve University School of Medicine, graduating in 1900. For many years he was on the Consulting Staff of the Youngstown Hospital. In 1923 he became a member of the American Congress on Internal Medicine, and when the Congress was merged with the American College of Physicians in 1926, he automatically became an Associate of the College and maintained that status the rest of his life. He retired from the practice of medicine about the end of 1948. In his last letter to the College he said in part, "Of all the associations to which I have belonged in my many years of practice, I have enjoyed and received the most benefits from the American College of Physicians."

DR. THOMAS JOSEPH WALSH

Thomas Joseph Walsh, M.D., LL.D., F.A.C.P., born in Buffalo, New York, 1878; graduated from the University of Buffalo School of Medicine, M.D., 1902; died on May 19, 1950, of coronary thrombosis.

Dr. Walsh was associated with the University of Buffalo School of Medicine for 25 years. When he resigned in 1940 he was Associate Professor of Medicine. He was the Chief Attending Physician at the Buffalo Hospital of the Sisters of Charity which position he held for nearly 30 years. He was also Chief of the Medical Service of the Louise de Marillac Hospital; Attending Physician of the Edward J. Meyer Memorial Hospital; and Consulting Physician of the Mercy Hospital.

Because of his leadership and devotion to duty he was granted the honorary degree of Doctor of Laws by Niagara University in 1921. Dr. Walsh was a Fellow of the American Medical Association, Past President of the Buffalo Academy of Medicine, a Diplomate of the American Board of Internal Medicine with a special interest in Cardiology, a member of Alpha Omega Alpha, and a Fellow of the American College of Physicians since 1915.

Dr. Walsh was a highly respected physician in Buffalo. His advice and counsel were sought and respected by many young physicians whom he always encouraged. He will always be remembered by his colleagues and patients in Buffalo as a fine type of a gentleman who was generous, kind and considerate.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,
Governor for Western New York

LIEUTENANT COLONEL HEINZ KURANER (MC), U. S. ARMY

Lieutenant Colonel Heinz Kuraner (MC), U. S. Army, died in the crash of a U. S. Air Force transport on a mountain peak 37 miles southwest of Tokyo on April 21, 1950; aged 43.

Dr. Kuraner was born at Leavenworth, Kans., August 31, 1906, and received his A.B. degree (1928) and his M.D. degree (1931) at the University of Kansas. He interned at the Cleveland City Hospital and thereafter entered the Medical Corps of the U. S. Army, fulfilling many assignments at various Army posts, including the Fitzsimons General Hospital, the Gorgas Hospital in the Canal Zone and the Far East Command, Philippine Islands. During World War II he was Commanding Officer of the 61st Medical Training Battalion, of the 95th General Hospital in the European Theater, of the Third Station Hospital in the European Theater, of the 62nd General Hospital in the European Theater, of the 202nd and 121st General Hospitals also in the European Theater. He had been an Associate of the American College of Physicians since 1941.

DR. KARL SCHÄFFLE

Karl Schäffle, M.D., Fellow of the American College of Physicians since 1931, was born in Lewisburg, Pa., May 30, 1883, and died in Asheville, N. C., April 8, 1950, after nearly 30 years of the teaching and practice of diseases of the chest in western North Carolina.

Dr. Schäffle's medical education was at the University of Pennsylvania School of Medicine, where he received the M.D. degree in 1907. He was Assistant Instructor in Pathology, University of Pennsylvania School of Medicine, and was on the Staff of the Hospital of the University of Pennsylvania and the Presbyterian Hospital in Philadelphia while practicing medicine there from 1909 to 1914. He was then appointed Deputy Inspector of Dispensaries, Pennsylvania State Department of Health, becoming Chief of the Tuberculosis Division, and serving in that capacity until 1920. He then entered the U. S. Public Health Service, and was sent to Oteen, N. C., as Instructor in Postgraduate Courses in Tuberculosis.

After other assignments in this field, he returned to Oteen in 1925, established and edited the Veterans Bureau Medical Bulletin for its first year, and then joined the staff of the William LeRoy Dunn Memorial Clinic. He was a Diplomate of the American Board of Internal Medicine. Dr. Schäffle served as Governor for North Carolina and later as Regent of the American College of Chest Physicians. He served as Editor of the Bulletin of his County Medical Society, and was an Examiner for the Selective Service Board in Asheville, 1943–1944.

The extensive and enlightened work of Dr. Schäffle and other men of his time who devoted themselves to the clinical aspects of tuberculosis has left us a heritage which is almost invaluable. The public has become reasonably well-informed with relation to one of the most important chronic diseases.

ELBERT L. PERSONS, M.D., F.A.C.P.,
Governor for North Carolina

DR. ITALO FREDERICK VOLINI

In the early morning of June 24, 1950, while attending the meeting of the American Medical Association in San Francisco, Italo Volini died suddenly and peacefully from a myocardial infarction. Ten years earlier a similar episode had almost proved fatal. After taking time for an adequate convalescence, Dr. Volini had returned to a heavy schedule of work in the office, hospital and medical school. He continued to devote himself increasingly and most unselfishly to his family, his patients, and the many tasks he considered worthwhile.

Italo Frederick Volini was born May 24, 1893, in Chicago, received his B.S. degree from the University of Chicago in 1915 and his M.D. degree from Rush Medical College in 1917. He became an assistant in medicine at Loyola University School of Medicine in 1917 and was subsequently promoted to Professor of Medicine and Head of the Department of Medicine at Loyola in 1929, an appointment he held until his death. Dr. Volini was also Professor of Medicine of the Chicago College of Dental Surgery, Loyola University, Professor of Medicine at Cook County Graduate School of Medicine, a member of the Executive Board and Chairman of the Scientific Committee of the Hektoen Institute for Medical Research; attending physician, Cook County Hospital; Consultant, St. Mary's Hospital, Gary, Holy Cross, Columbus, Oak Park, St. Anne's, St. Bernard's and St. Elisabeth Hospitals. Dr. Volini served in World War I in the Medical Corps, U. S. Army; he served one year, 1946, on the Chicago Board of Education; in 1929 he received the decoration of the Crown of Italy and was named a chevalier by the king for his work among the Italians of Chicago; he was a diplomate of the American Board of Internal Medicine and, since 1929, a Fellow of the American College of Physicians.

Dr. Volini is survived by his wife, Marcella Ringwald Volini whom he married in 1925, and by all of his ten children. His extraordinary accomplishments were made possible by many factors: his own rugged constitution and seemingly inexhaustible energy, his calm imperturbability of manner, his capacity to think clearly and logically, his ability to put important things first, and the unfailing support found in the circle of his home. Italo's memory will live in the hearts of his family, his friends, his patients, and his students. Chicago medicine has lost a leader of outstanding ability and great personal charm. We shall miss him.

WALTER L. PALMER, M.D., F.A.C.P.,
Governor for Northern Illinois

DR. C. CHARLES BURLINGAME

Dr. C. Charles Burlingame, F.A.C.P., died in Leicester, England, on July 22, 1950, following an attack of coronary thrombosis which occurred a few days before. He had gone to England two weeks before to attend the meeting of and receive an honorary membership from the Royal Medico-Psychological Association.

Dr. Burlingame was born October 27, 1885, in Rockford, Ill., son of the late Charles Henry Camlin and Ella Dagwell Burlingame. His wife, Mrs. Ruth B. P. Burlingame, survives him.

He was graduated from General Medical College of Chicago in 1908. He came to the Institute of Living, then known as the Hartford Retreat, in 1931. Prior to that he had served on the staff of the Westboro State Hospital in Massachusetts, acting director at Fergus State Hospital (Minn.); medical officer at Cheney Brothers, Inc., in Manchester, Conn.; executive officer at Columbia University Presbyterian Medical Center, and had practiced psychiatry in New York City.

During World War I he served overseas as head of the Bureau of Hospital Administration of the American Expeditionary Forces. At the conclusion of the war he served with the American Red Cross in France as director of the Medical and Surgical Department. During World War II he served as consultant in psychiatry to the Secretary of War.

He lived a full, active, energetic, untiring life. His likes and dislikes were equally strong. He probably could be classed as a psychiatric heretic having little time for the fads or fancies of psychiatry and less time for the writings of untrained psychiatrists. He constantly called for a change in the term psychiatrist to medical psychologist.

He was a life member of the American College of Physicians, President-Elect of the Connecticut State Medical Society, Fellow of the American Medical Association, a certificant of the American Board of Psychiatry and Fellow of the American Psychiatric Association.

He had been honored for his war work by the governments of the United States, France, England, Poland and Czechoslovakia.

And so comes to an end the life of a very unusual man. A life filled with accomplishments. His loss is great and he will be greatly missed at the Institute of Living in Hartford, by medicine in Connecticut and in the United States.

THOMAS P. MURDOCK, M.D., F.A.C.P.,
Governor for Connecticut

DR. ARCHIBALD EVANS CARDLE

On the evening of June 23, 1950, Dr. Archibald Evans Cardle was returning from the East on a Northwest Airlines plane preparatory to meeting his wife in Minneapolis

and proceeding on to San Francisco as a delegate to the American Medical Association. But Dr. Cardle, along with 57 other persons, was lost in Lake Michigan when the airliner crashed during a storm. Thus, at the age of 51 years, Medicine lost a leader, and his friends in Minnesota were suddenly deprived of a warmhearted and congenial associate.

Born in Oklahoma in 1899, Dr. Cardle received his medical degree from the University of Iowa Medical School in 1923. He interned at the Maryland General Hospital in Baltimore, and continued his training with a residency at the Minneapolis General Hospital. He practiced medicine in Minneapolis since 1925. He was a diplomate of the American Board of Internal Medicine, and elected to Fellowship in the American College of Physicians in 1935. He was Clinical Assistant Professor of Medicine at the University of Minnesota Medical School. He had staff appointments in numerous Minneapolis Hospitals. He was a member of the Minneapolis Academy of Medicine, Minnesota Society of Internal Medicine, and at the time of his death, he was Secretary of the Minnesota Academy of Medicine. All during his professional life, Dr. Cardle was active in organizational affairs in Medicine. He was an officer of the Hennepin County Medical Society, and served as a delegate to the Minnesota State Medical Association. In 1947, he was chosen President of the State society. He was the youngest president in the history of the Association. His capacity for leadership was recognized in that he was then elected as a delegate to the American Medical Association. Dr. Cardle is survived by his widow and two children.

Wesley W. Spink, M.D., F.A.C.P.,
Governor for Minnesota

DR. ALFRED MEYER

Dr. Alfred Meyer, F.A.C.P., of New York City, died in Ogunquit, Maine, at the age of ninety-six, on July 14, 1950. Dr. Meyer, who was the oldest alumnus of Columbia University, died peacefully in his sleep at his summer home.

He had had a long and varied career. He was born in New York City in 1854 and graduated from Columbia University College of Physicians and Surgeons in 1877. He served his internship at Mt. Sinai Hospital and later studied abroad. In 1880 he began the pratice of medicine and was very active for a number of years thereafter. He was an accomplished musician and some of his fellow physicians described his diagnostic methods, particularly as regards the chest, as a "piano-tuning operation." He retired from active practice in 1930 at which time he was a consulting physician at Mt. Sinai and Montefiore Hospitals. Dr. Meyer was a member of the New York Thoracic Society, New York Tuberculosis and Health Association, a Fellow of the New York Academy of Medicine, and had been a Fellow of the American College of Physicians since 1919.

He was a crusader in the field of tuberculosis and was the founder of the Committee on Prevention of Tuberculosis of the Charity Organization which later became the New York Tuberculosis and Health Association. He also was instrumental in the organization of the city's tuberculosis sanatorium at Otisville, and the State Institution at Raybrook; also, the Montefiore Hospital Country Sanatorium at Bedford Hills, N. Y.

Dr. Meyer's career was a notable one and it is sad to record the passing of such a distinguished doctor.

Asa L. Lincoln, M.D., F.A.C.P.,
Governor for Eastern New York

ABSTRACTED MINUTES OF THE BOARD OF REGENTS

BOSTON, MASS.

APRIL 21, 1950

The third and final meeting of the Board of Regents, during the 31st Annual Session of the American College of Physicians, was held Friday, April 21, 1950, with Dr. William S. Middleton presiding as President, with Mr. E. R. Loveland acting as Secretary and seventeen Regents in attendance.

Dr. Middleton presented the following memorial, following which the Board rose and stood in respectful silence, and then directed that it be published in the ANNALS OF INTERNAL MEDICINE and a copy sent to Mrs. Richards:

"In the sudden death of Dr. G. Gill Richards, F.A.C.P., last evening, the American College of Physicians lost a devoted member. He was born in Salt Lake City, Utah, in 1883 of pioneer parents, his grandfather having been a scout who accompanied Brigham Young in the migration to Utah. He was always true to the tenets of his faith; a real Christian gentleman. One had only to observe the hospitality of his home and associate with him professionally and socially to realize he was 'of the chosen.' He graduated from University and Bellevue Hospital Medical College in 1906. His professional career was spent in the city of his birth. On the Utah scene, Gill Richards was without question the most powerful figure in medicine. His efforts were directed toward the improvement of the practice of medicine in the Rocky Mountain States, and particularly in Utah.

"At the time of his death he was Clinical Professor of Medicine, and had been for years the motivating force in bringing the University of Utah College of Medicine to its present high estate. As a matter of fact, he personally considered that as his greatest contribution to medicine.

"In our intimate relations with the American Board of Internal Medicine, we came to appreciate Gill Richards' integrity of mind and action. He had a peculiar bent toward the work of the Board. No candidate ever passed a Gill Richards' examination who could not take a true history and pursue an accurate examination. He was almost a religious zealot in these two objectives.

"In the home he was a gracious host; a kind friend, and a worthy representative of his church and of this College. In the affairs of the American College of Physicians Gill Richards took an active part from 1920. Thirty years were given by him to this organization—first as a Fellow, then Governor, Regent and Vice President. We have indeed lost one of our most able, most representative Fellows."

Dr. James R. Bell, of the Cleveland Academy of Medicine, and Mr. Edward C. Brennan, of the Cleveland Convention Bureau, appeared before the Board and presented an invitation to the College to hold its 1952 Annual Session in that City. Other invitations were discussed and analyzed, and a resolution was adopted accepting Cleveland's invitation and setting the date for April 21–25, 1952.

The Secretary then reviewed the Minutes from the preceding meeting of the Board of Regents, which were approved as presented. A matter referred from the previous meeting to this meeting was that concerning the College membership in Cuba, which had been presented by Dr. Turner Z. Cason. After general discussion, a resolution was adopted, expressing to Dr. Cason the appreciation of the Board of Regents of the effort he has made over the years to maintain proper relationships between the Fellows in Cuba and the Fellows in Florida, and to request him to confer with the present Governors, Dr. William C. Blake, of Florida, and Dr. José J. Centurión, of Cuba, with respect to further steps that may be taken.

In accordance with regulations of the By-Laws, Dr. George Morris Piersol and Dr. William D. Stroud were reëlected Secretary-General and Treasurer, respectively, for the year 1950–51, and the Executive Committee of the Board of Regents for the coming year was elected, consisting of:

William S. Middleton, Chairman, Madison, Wis.
Maurice C. Pincoffs, Baltimore, Md.
George Morris Piersol, Philadelphia, Pa.
William D. Stroud, Philadelphia, Pa.
Edward L. Bortz, Philadelphia, Pa.
Reginald Fitz, Boston, Mass.
William S. McCann, Rochester, N. Y.
Hugh J. Morgan, Nashville, Tenn.
Cyrus C. Sturgis, Ann Arbor, Mich.

Likewise, in accordance with regulations of the By-Laws, or specific provisions of the Board of Regents, standing committees were appointed for the coming year. In view of the fact that the personnel of these committees has already been published in the June issue of this journal, it is not herein repeated.

At the request of President Middleton, the Chairman of the Board of Governors, Dr. Walter L. Palmer, presented the following report:

"We held an indoctrination meeting of the new Governors last evening, at which were present President Middleton, Dr. Piersol, as Chairman of the Committee on Credentials, Mr. Loveland, as Executive Secretary, and I, as Chairman of the Board of Governors. I believe it was a very worth while meeting from the standpoint of informing new Governors of their duties, particularly with respect to the handling of candidates. I think it would be a good plan to continue this orientation meeting each year and to make it more or less official. New Governors were invited to attend the meeting of the Committee on Credentials preceding the Annual Session, in order that there may be a wider discussion of the criteria of membership."

A resolution was adopted approving the recommendations of Dr. Palmer.

Dr. Ralph A. Kinsella, St. Louis, was elected General Chairman of the Thirty-second Annual Session, to be held in St. Louis, Mo., April 9–13, 1951.

President Middleton spoke briefly concerning the Technical Exhibits of medical societies, with special reference to that of the American College of Physicians. He felt that in the academic field of medicine we are confronted with the inroads of commercial houses, so that today the practice of medicine is considerably dictated by pharmaceutical houses and their detail men. He said, further, in part, "I have been amazed at the quality of the work that goes into the several trade journals. It is a matter of comment and tremendous influence in the practice of medicine throughout this country; it is not, by and large, our scientific gatherings, not our scientific journals, not importantly our institutions of medical education that are dictating the treatment in the by-ways and hedges of this country, but the pharmaceutical houses. . . . I feel the American College of Physicians in its dignity could well afford to require that commercial exhibits be placed on the highest possible plane—not pure exhibits, but demonstrations and scientific qualities added that might definitely raise them from their present levels. . . ."

An invitation was presented on behalf of the City of Minneapolis and the State of Minnesota for the College to hold its 1953 Annual Session in Minneapolis. It was a complete and detailed invitation, received from every medical group of any character in the State of Minnesota, and it was initiated by one of the College's former Presidents, Dr. S. Marx White. The invitation was received with interest

and appreciation, but the Board thought it appropriate not to select the meeting city three years ahead, especially at current costs and rental prices. It is anticipated the invitation will be acted upon at the Annual Session in St. Louis in 1951.

Dr. Edward L. Bortz proposed for consideration an Annual Session of the College in Atlantic City some time in the future, pointing out that with the introduction of color television, clinics could be televised from Philadelphia or Baltimore, in view of the fact that adequate facilities for clinics are not available in Atlantic City, and that the program could be expanded additionally in the line of more lectures, panel discussions and other features. Dr. Cyrus C. Sturgis joined in that suggestion.

President Middleton bespoke the support and coöperation of all members of the Board during his Presidency of the College, and asked for advice and help in connection with the preparation of the program for the next Annual Session.

Adjournment.

Attest: E. R. Loveland,
Secretary

ANNUAL BUSINESS MEETING

Boston, Mass.

April 20, 1950

The Annual Business Meeting for 1950 of the American College of Physicians, during the 31st Annual Session, was held in Grand Hall, Mechanics' Building, Boston, Mass., Thursday, April 20, 1950, with President Reginald Fitz presiding.

The President announced a quorum present, in view of the fact that approximately two thousand members were in attendance.

Mr. E. R. Loveland, Secretary, read abstracted Minutes of the preceding Annual Business Meeting, which were approved as read.

The Treasurer, Dr. William D. Stroud, presented the following report, which, by motion duly seconded and carried, was accepted:

"Mr. President, Masters and Fellows of the College: The detailed statements of operation of the College for 1949, along with the Certified Public Accountant's audit, will be published in the May Issue of the Annals of Internal Medicine.

"During the year 1949 the College added to its General Fund $40,052.07; to its Endowment Funds $24,484.02, a total of $64,536.09. The College received a gift in trust of $2,500.00, being the third installment on an educational trust fund of $10,000.00 subscribed by Dr. A. B. Brower, one of our Fellows. The final installment of $2,500.00 was received at this meeting.

"The gross assets of the College, as of December 31, 1949, amounted to $747,743.70, divided as follows:

General Fund	$420,985.54
Endowment Fund	308,706.08
James D. Bruce Fund	10,395.83
A. Blaine Brower Fund	7,656.25
	$747,743.70

"The College operated entirely within its budget for the year. Its investments are supervised by an Investment Counselor and the Committee on Finance and are carefully reviewed periodically. As of December 31, 1949, the College held investments at book value totalling:

Endowment Fund	$321,255.91
General Fund	191,572.70
	$512,828.61

"The current market value of these investments shows an appreciation of $41,884.47. The current average yield on all investments is 4.28%.

"The Board of Regents has approved a budget for 1950 calling for an estimated income of $240,900.00 and an estimated expenditure of approximately $196,000.00, leaving an anticipated balance of approximately $44,000.00. The financial policies of the College continue to be conservative at all times."

Respectfully submitted,
WILLIAM D. STROUD, *Treasurer*

Mr. E. R. Loveland presented the following annual report of the Executive Secretary, which was by resolution accepted:

"Mr. President, Fellows and Masters of the College: The report of the Executive Secretary is supplementary to those of the President, the Treasurer and the Secretary-General.

"It is an abiding satisfaction to see the College continuing and expanding its services to its members and to the causes of Internal Medicine and its affiliated fields. 1949 was no exception to the policies that have been established as the foundation of our organization. During the year we conducted 22 formal Regional Meetings, largely of the single State character, but in several instances of the multi-State character, and it appears probable that even more of these Regional Meetings will be conducted during 1950. The meetings are attended by a large portion of its members and a goodly number of non-members, especially young men who have as their objective eventual membership in the College.

"The ANNALS OF INTERNAL MEDICINE has continued to grow as the outstanding journal in Internal Medicine of North America. The circulation increased during the past year to approximately 13,500 copies per month, an increase of approximately 13%. The journal goes to every country in the World.

"As of October 1, 1949, the College published a completely revised Directory, the first since prior to the War in 1941. Due to exceptionally heavy publication costs, because of the enormity of the task and rising costs of printing, the Board of Regents authorized the publication of this Directory on condition that members should be willing to contribute $4.00 toward the cost in case they desired a copy. The requisite number was oversubscribed. It is anticipated that a Supplement will be published during the summer of 1950, and a complete revision issued every two years, and that future publications of the Directory may be given to all members in good standing without charge.

"One year ago the Boards of Regents and Governors, appreciating the fundamental desirability of conducting the Annual Sessions on their present plan and plane, determined to restrict the attendance more largely to the members of the College. This has been instrumented by requiring non-members to be sponsored by members of the College and by increasing the non-member attendance fee to $25.00, which includes not only the privileges of the meeting, but the proceedings as published during the succeeding year in the ANNALS OF INTERNL MEDICINE. It will require some analysis at the end of this meeting to determine in what measure this plan has been successful. We do not yet have a breakdown of the current registration with regard to members and non-members, but it is certain that a much larger number of non-members would have been in attendance at this meeting without these restrictions and that the facilities to accommodate members would have been much more reduced.

"The current meeting is the 24th Annual Session at which your Executive Secretary has functioned. The activities of the College have increased many, many fold during these years. We are determined to maintain, to the best of our ability and ideals, the principles of promptness, efficiency and service, and I am especially gratified that your Board of Regents has authorized some important additional service in my office.

"The members-at-large should appreciate the great and unselfish service contributed by their Officers, Regents and Governors who serve without remuneration or special prerogatives—and serve exceedingly well.

"At this particular moment I especially want to express my appreciation for the ever-ready help and advice of President Fitz during the past year, and I also want to thank Dr. Keefer and the many, many Committee Chairmen and members who have helped in the preparation of this meeting.

"We have just received from the Registration Desk a report that the total registration to this time is 4,726 of which 840 are ladies.* Last year it was over 5,600 but we are sure that there is a larger proportion of members this year than non members, although there are many non-members."

Respectfully submitted,
E. R. LOVELAND, *Executive Secretary*

Dr. George Morris Piersol presented the following annual report of the Secretary-General, which by resolution was accepted:

"Mr. President, Regents, Governors, Masters and Fellows of the College: This report will cover certain salient matters of especial interest to you.

"Membership: Since the last Annual Session of this College there have been elected 1 Master, 300 Fellows and 473 Associates, which brings the total membership to 6,937, divided as follows:

Masters	13
Fellows	4,973
Associates	1,951
Total	6,937

"We direct to your attention certain interesting analyses that are depicted by charts and displayed at the College Booth near the Registration Headquarters. Those analyses were prepared up to the opening of this Session and do not cover the new members elected at this meeting.

"Life Members: During the past year 78 Fellows have become Life Members of the College, bringing the total to 863, of whom 75 are deceased, leaving a balance of 788.

"Deaths: During the past year we have lost by death 2 Masters, 70 Fellows and 11 Associates. Their names and records are recorded in the Archives of the College.

"Postgraduate Courses: The Advisory Committee on Postgraduate Courses of the Board of Governors and the Committee on Educational Policy of the Board of Regents organized and conducted during 1949 a total of 17 Courses, with a registration

* Final Analysis of Registration:

Members	2,091
Guest Physicians	1,225
Guest Non-Physicians	42
Exhibitors	591
Ladies	840
	4,789

of 1,022 physicians. Each year an effort is made to improve the quality of instruction, to expand the field of study and to increase and diversify the institutions and geographical locations where the courses are given.

"*Fellowships:* The College is maintaining at the present time 7 active Research Fellowships and has voted 6 new Research Fellowships starting July 1, 1950. The annual budget for this Fellowship Program is approximately $20,000.00. The work of these Fellows and the ensuing results are carefully observed, with a view to evaluating the program and to act as a guide in the future.

"Through the coöperation of the W. K. Kellogg Foundation, a Latin-American Fellowship Program was initiated during the spring of 1949, affording an opportunity for the training of Latin-American young men for a career of teaching and research in their home lands. Already 8 Latin-American Fellowships have been awarded. These young men have come to the United States or are soon to arrive. As a general policy they are given several months of indoctrination in American medical methods in a special course at Cornell University, and thereafter are placed by our Committee on Fellowships under the preceptorship of the most competent men in their particular fields. At the conclusion of their period of fellowship, they will return to their medical schools where appointments on the faculty or in research departments await them. Those who are already at work in this country have shown genuine appreciation and satisfactory progress, and it is to be expected that the influence and merit of this program will be far-reaching in the future.

"As gratifying as may be the abovementioned educational activities of the College, its Annual Sessions, perhaps, are the most significant and far-reaching contribution of the College. This Session in Boston is a further outstanding example of what may be accomplished by a year's well co-ordinated effort. We are mindful of our great debt to those who have made this, the 31st Annual Session of the College, possible."

Respectfully submitted,
GEORGE MORRIS PIERSOL, *Secretary-General*

DR. PIERSOL: "Now, Mr. President, you have guided the destiny of this organization through the past year and have carried out its purposes with good judgment and exceptional ability. We, who have had the privilege to be closely associated with you in the conduct of the College, are keenly aware of the never failing courtesy, coöperation and forbearance that have marked your every act. It is, therefore, our desire to express to you in some enduring manner our appreciation and affection. On behalf of your fellow Officers, the Regents and the Governors of the American College of Physicians, it is our pleasure at this time to present you with this Gavel." (Applause.)

PRESIDENT FITZ: "Thank you for this Gavel of the College. It is one of the greatest distinctions to come to any one. For my luncheon today I happened to have a sandwich made of a very thin slice of ham, supported on both sides with two substantial slices of bread. During my Presidency I have felt as though I were a very thin slice of ham and supported very well on both sides, first by my predecessor, former President Walter W. Palmer, and by my successor, Dr. William S. Middleton. I regard Dr. Palmer as one of the finest Presidents the College has had, a man whom I have known for a long period of time, whom I have always admired, and whose Presidency was characterized by his guidance, force of character and great interest in the task. The person who succeeds me is another substantial slice of bread, whom I have known for a great many years, and all I can say is the longer I have known him the more I have secured in wisdom through his knowledge and character. Therefore, it is a great pleasure for me to hand over the Gavel of office and introduce to you the new President of the American College of Physicians, Dr. William S. Middleton, of Madison, Wis." (The audience arose and there was prolonged applause.)

PRESIDENT WILLIAM S. MIDDLETON: "Mr. President, Masters and Fellows of the American College of Physicians, may I say that the present status of the American College of Physicians is not an astronomical phenomena. It has depended upon the devoted services of many of the members over many years. It is obvious, therefore, that in assuming the responsibilities and the high honor of this office, I should call upon you for your continuing, sustaining and augmentable support. I shall need it.

"Before we pass on to the further business of the day, I should like to bring to your attention certain reflections upon some of the problems of the American College of Physicians. The Fellowship of the College is indeed restricted, and appropriately so. Let us make it an aristocracy based upon intellectual integrity, human service and professional or scientific attainment. Let there never arise the question of prejudice on the basis of sex, race, creed or politics. In a word, let us go forward as the American College of Physicians. The matter of age has been raised in our councils, and it is apparent that we will depend upon the youth of medicine to sustain our group. We have made material progress in this direction through the Research Fellowships of the College, through our Annual and Regional Meetings. I believe the Fellows of the College will come from these sustained groups, and the men of the future of American Medicine will be the Fellows and Masters of this College. These physicians of today, who are to make medicine of America in the future, will obviously arise from this generation.

"In the international field, we have appreciated, through recent action, our responsibility, long neglected in the American College of Physicians. We have announced the Latin-American Fellowships and initiated into our Honorary Fellowship a British confrere.

"I am going to introduce now a matter that is highly personal in action, because I want to tell you that in these College meetings I have been impressed by the group of commercial exhibitors, and I use the term 'commercial' advisedly. We have had careful censorship of these exhibits, but it is my personal reaction that the College would do well to be even more careful in this direction in the future. It may be impossible to limit the demonstrations, but at least the dignity of this particular phase of our Annual Session should be on such a plane that the 'tail does not wag the dog.' I, for one, should be in favor of casting the 'money-changers from the Temple.'

"And, finally, a matter that must come to the attention of every thinking physician in these parlous times. The deliberations and the assemblies of the American College of Physicians have been a reflective oasis in the burning sands of medical controversy. Let us protect this position carefully. I am first to admit to every physician and to every American citizen their rights. I feel that we do well to spare ourselves the asperity that may arise from discussions of a political nature. Let us bear in mind the admonition of Shakespeare, *'Mud not the fountain that gave drink to thee'.*" (Applause.)

PRESIDENT MIDDLETON (Continuing): "The Secretary will now present some amendments to the Constitution and By-Laws."

MR. E. R. LOVELAND: "The Committee on Constitution and By-Laws recommends the adoption of the following amendments to the By-Laws, providing that the Surgeon General of the Medical Service of the United States Air Force, which is now a separate unit, shall be a member of the Board of Governors, thus authorizing him to be the final endorser of all candidates for membership in the College from that Service; the same as is the case at present with the Surgeons General of the U. S. Army, U. S. Navy, U. S. Public Health Service and the Medical Director of the Veterans Administration. The changes required are as follows:

> "By-Laws, Article IV, Board of Governors, section (1), line 7 to read, 'Board of Regents; one each from the United States Army, Navy, *Air Force,* Public. . . .'

"By-Laws, Article V, Election of Fellows, section (2), line 6 to be revised to read, 'he resides, or by the Surgeon General of the Army, Navy, *Air Force*, or Public Health. . . .'

"By-Laws, Article VII, Election of Associates, section (2), line 7 to read, 'Navy, *Air Force* or Public Health Service or the Medical Director of the Veterans. . . .'".

On motion duly made and seconded and carried, it was voted that the above changes, as suggested by the Committee on Constitution and By-Laws and approved by the Board of Regents, be hereby adopted.

PRESIDENT MIDDLETON: "A resolution has been offered to the Board of Regents and has received its approval, as follows:

'The American College of Physicians is dedicated to progress in the art and science of medicine to the end that the best possible medical care may be made available to all the people. It welcomes plans that will advance these aims. It is the conviction of the American College of Physicians, however, that its objectives can be accomplished best in a free society unhampered by governmental control.'" (Applause.)

The resolution was offered for action, and upon motion duly made, seconded and carried, it was voted that the resolution as read be adopted unanimously. (Applause.)

PRESIDENT MIDDLETON: "The next order of business is the report of the Committee on Nominations by Dr. Harold H. Jones, Chairman."

DR. HAROLD H. JONES: "Mr. President, the Committee on Nominations, appointed in accordance with the Constitution of the College, places in nomination the following names for the Elective Officers of the College:

President-Elect ..... Dr. Maurice C. Pincoffs, Baltimore, Md.

A motion was duly made, seconded and carried, providing that nominations be closed and that the Secretary cast one ballot for the election of Dr. Maurice C. Pincoffs as President-Elect of the College.

Dr. JONES (Continuing):

"First Vice President ..... Dr. Ernest H. Falconer, San Francisco, Calif.
Second Vice President ..... Dr. Edgar Hull, New Orleans, La.
Third Vice President ..... Dr. Arthur T. Henderson, Montreal, Que."

On motion by Dr. Hugh J. Morgan, duly seconded and unanimously carried, these nominees were elected by acclamation.

DR. JONES (Continuing): "The Committee places in nomination the following five names for election as Regents of the American College of Physicians for a term expiring in 1953:

Dr. A. B. Brower, Dayton, Ohio
Dr. Alex. M. Burgess, Sr., Providence, R. I.
Dr. Reginald Fitz, Boston, Mass.
Dr. George H. Lathrope, Newark, N. J.
Dr. Cyrus C. Sturgis, Ann Arbor, Mich."

On motion duly made, seconded and unanimously carried, nominations were closed and the above five nominees were elected as Regents of the College.

DR. JONES (Continuing): "The Committee places in nomination as Governor for Southern Illinois, for term expiring in 1952, to conclude the unexpired term of Dr. Cecil M. Jack, deceased, the name of

Dr. Charles H. Drenckhahn, Urbana."

On motion duly made, seconded and carried, nominations for this office were closed and unanimous vote cast by the Secretary for the election of Dr. Drenckhahn.

DR. JONES (Continuing): "The Committee places in nomination the names of the following men as Governors of the American College of Physicians, for term expiring in 1953:

Dr. Arless A. Blair, Fort Smith.....ARKANSAS
Dr. Dwight L. Wilbur, San Francisco.....CALIFORNIA (Northern)
Dr. Benjamin F. Wolverton, Cedar Rapids.....IOWA
Dr. Thomas P. Findley, New Orleans.....LOUISIANA
Dr. Douglas Donald, Detroit.....MICHIGAN
Dr. Wesley W. Spink, Minneapolis.....MINNESOTA
Dr. Ralph A. Kinsella, St. Louis.....MISSOURI
Dr. Lawrence Parsons, Reno.....NEVADA
Dr. Harry T. French, Hanover.....NEW HAMPSHIRE
Dr. Edward C. Klein, Jr., Newark.....NEW JERSEY
Dr. Elbert L. Persons, Durham.....NORTH CAROLINA
Dr. Robert B. Radl, Bismarck.....NORTH DAKOTA
Dr. Herman A. Lawson, Providence.....RHODE ISLAND
Dr. Robert Wilson, Jr., Charleston.....SOUTH CAROLINA
Dr. Ellsworth L. Amidon, Burlington.....VERMONT
Dr. Charles M. Caravati, Richmond.....VIRGINIA
Dr. George H. Anderson, Spokane.....WASHINGTON
Dr. Paul H. Revercomb, Charleston.....WEST VIRGINIA
Dr. Arthur B. Walter, St. John, N. B.....MARITIME PROVINCES
Dr. Walter de M. Scriver, Montreal .....QUEBEC
Dr. José J. Centurión, Havana.....CUBA"

On motion regularly made, seconded and carried, nominations were closed and the Secretary instructed to cast unanimous ballot for the election of the nominees presented.

DR. JONES (Continuing): "The Committee on Nominations wishes to announce that under the revisions of the By-Laws, providing that the Surgeon General of the United States Air Force shall become a member of the Board of Governors, representing that Service. Major General Harry G. Armstrong (MC), USAF, will at this time become the official Governor of the United States Air Force."

PRESIDENT MIDDLETON: "At this time I shall appoint Dr. Charles F. Moffatt and Dr. Walter B. Martin to escort our new President-Elect, Dr. Maurice C. Pincoffs, to the platform." (President-Elect Pincoffs was escorted to the platform amid prolonged applause.)

PRESIDENT-ELECT MAURICE C. PINCOFFS: "Mr. President, Masters and Fellows of the College: Need I tell you that I very deeply appreciate this honor, to have in prospect that one day my name may be entered in the Archives of the College as one of the succession of the distinguished men who have held the Presidency? I am well aware of the responsibilities that rest upon the President's shoulders, and I assure you that during this coming year I shall carefully understudy your President in the hope that with the support of the Regents, the Governors, and particularly with the support of all of you the year in which I shall hold the Presidency may be one in which the standards and traditions of the College will be maintained and its development continued." (Applause.)

PRESIDENT MIDDLETON: "I wish to announce that the 1951 Annual Session will be held in St. Louis, Mo., April 9–13.

"Is there anything further to come before this meeting?"

DR. EDWARD L. BORTZ: "Mr. President, I wish to offer the following resolution:

"To our distinguished leader and President, Dr. Reginald Fitz, for the inspiration of his guidance during the past year, as well as during this Annual Session;

"To his Chief of Staff, General Chairman Chester S. Keefer, for a magnificent program;

"To the Chairmen of their local Committees:

Dr. Theodore L. Badger, Chairman of the Committee on Auditorium
Dr. Lewis Dexter, Chairman of the Committee on Clinics
Dr. Ellsworth T. Neumann, Chairman of the Televised Clinics Committee
Dr. Richard P. Stetson, Chairman of the Committee on Entertainment
Dr. Francis C. Lowell, Chairman of the Committee on Transportation and Hotels
Dr. Joseph F. Ross, Chairman of the Committee on Panel Discussions
Dr. John F. Conlin, Chairman of the Committee on Publicity

and to the individual members of each of those Committees;

"To Mrs. George W. Thorn, Chairman of the Committee on Ladies' Entertainment, and all of her worthy and capable colleagues;

"To Mr. James A. Morrison, Manager of the Convention Bureau of the Boston Chamber of Commerce;

"To all of these and many others, individually and collectively, our heartfelt thanks again for their manifold contributions to the success of this memorable meeting and for their most generous hospitality."

PRESIDENT MIDDLETON: "I know that this expresses the sentiment of each and everyone of us, and it may be best expressed by your applause." (Applause.)

Adjournment: 2:50 p.m.

Attest: E. R. LOVELAND,
Secretary

MINUTES OF THE BOARD OF GOVERNORS

BOSTON, MASS.

APRIL 19, 1950

A regular meeting of the Board of Governors, the second during the 31st Annual Session, convened at 12:30 p.m., April 19, 1950, at Mechanics' Building, Boston, Mass., with Dr. Walter L. Palmer presiding and with Mr. E. R. Loveland acting as Secretary. The following were in attendance:

Governors:

Arless A. Blair, Fort Smith .....ARKANSAS
Dwight L. Wilbur, San Francisco .....CALIFORNIA (Northern)
Benjamin F. Wolverton, Cedar Rapids ..IOWA
Edgar Hull, New Orleans .....LOUISIANA
Douglas Donald, Detroit .....MICHIGAN
*H. L. Smith, Rochester .....MINNESOTA
Ralph A. Kinsella, St. Louis .....MISSOURI
Harry T. French, Hanover .....NEW HAMPSHIRE
George H. Lathrope, Newark .....NEW JERSEY
Paul F. Whitaker, Kinston .....NORTH CAROLINA
Robert B. Radl, Bismarck .....NORTH DAKOTA
Herman A. Lawson, Providence .....RHODE ISLAND
Robert Wilson, Jr., Charleston .....SOUTH CAROLINA
Ellsworth L. Amidon, Burlington .....VERMONT
*Charles M. Caravati, Richmond .....VIRGINIA
George Anderson, Spokane .....WASHINGTON
Delivan A. MacGregor, Wheeling .....WEST VIRGINIA
*N. S. Skinner, St. John, N. B. .....MARITIME PROVINCES
Arthur T. Henderson, Montreal .....QUEBEC
*Angel Vieta y Barahona, Havana .....CUBA
E. Dice Lineberry, Birmingham .....ALABAMA
Leslie R. Kober, Phoenix .....ARIZONA
Lemuel C. McGee, Wilmington .....DELAWARE
William C. Blake, Tampa .....FLORIDA
Carter Smith, Atlanta .....GEORGIA
Samuel M. Poindexter, Boise .....IDAHO
Walter L. Palmer, (Chairman),
Chicago .....ILLINOIS (Northern)
J. Murray Kinsman, Louisville .....KENTUCKY
Richard S. Hawkes, Portland .....MAINE
Wetherbee Fort, Baltimore .....MARYLAND
John G. Archer, Greenville .....MISSISSIPPI
Harold W. Gregg, Butte .....MONTANA and WYOMING
Asa L. Lincoln, New York .....NEW YORK (Eastern)
Charles A. Doan, (Vice-Chairman),
Columbus .....OHIO
Howard P. Lewis, Portland .....OREGON
David W. Carter, Jr., Dallas .....TEXAS
Karver L. Puestow, Madison .....WISCONSIN
Rafael Rodriguez-Molina, San Juan ....PUERTO RICO

* Alternate.

John W. Scott, Edmonton ..... Alberta and British Columbia
Charles H. A. Walton, Winnipeg ..... Manitoba and Saskatchewan
Leland Hawkins, Los Angeles ..... California (Southern)
Ward Darley, Denver ..... Colorado
Thomas P. Murdock, Meriden ..... Connecticut
John Minor, Washington ..... District of Columbia
Charles H. Drenckhahn, Urbana ..... Illinois (Southern)
James O. Ritchey, Indianapolis ..... Indiana
William C. Menninger, Topeka ..... Kansas
Joseph D. McCarthy, Omaha ..... Nebraska
Edward C. Reifenstein, Sr., Syracuse ... New York (Western)
Wann Langston, Oklahoma City ..... Oklahoma
Thomas M. McMillan, Philadelphia .... Pennsylvania (Eastern)
Charles W. Morton, Pittsburgh ..... Pennsylvania (Western)
Charles F. Morsman, Hot Springs .... South Dakota
William C. Chaney, Memphis ..... Tennessee
*Frederick L. Giles, Honolulu ..... Hawaii
Herbert K. Detweiler, Toronto ..... Ontario
Gilbert M. Stevenson, Ancon ..... Republic of Panama and the Canal Zone
*Paul S. Fancher ..... United States Army
*L. R. Newhouser ..... United States Navy
*Otis L. Anderson ..... United States Public Health Service
*Arden Freer ..... United States Veterans Administration
Harry G. Armstrong ..... United States Air Force

Guests:

Reginald Fitz ..... President
William S. Middleton ..... President-Elect
Edward L. Bortz ..... Regent
LeRoy H. Sloan ..... Regent

The Secretary reviewed the Minutes of the preceding combined meeting of the Regents and Governors, held on April 16, and then read abstracted Minutes of the two preceding meetings of the Board of Governors, held at New York City in 1949.

President Fitz, amid applause, thanked the members of the Board of Governors for their enthusiasm and assistance in making the Boston Session an outstanding success.

President-Elect Middleton spoke briefly emphasizing the importance he had observed not only of the Annual Session but especially of the numerous regional meetings conducted by the Governors in all parts of the country, and told the Board that the College must expect the Governors to carry the torch for the College in all quarters of the land. He bespoke their support of his endeavors during his presidency.

Chairman Palmer: Thank you very much, Dr. Fitz and Dr. Middleton, for attending our meeting and bringing us a message.

The next item is the election of a Governor to serve on the Committee on Credentials in the place of Dr. George H. Lathrope, whose term expires with this meeting. In placing this matter before you, I think I should tell you there are two other members of the Credentials Committee, Dr. J. Murray Kinsman, of Louisville, Ky., and Dr. Robert Wilson, Jr., of Charleston, S. C., who are representatives of the

* Alternate.

Board of Governors. The representatives on that Committee from the Board of Regents are Dr. LeRoy H. Sloan, Chicago, Dr. Wallace M. Yater, Washington, and Dr. George Morris Piersol, Philadelphia.

I shall now be glad to entertain the nomination of a representative from the Board of Governors on the Committee on Credentials.

Dr. George H. Lathrope nominated Dr. Lemuel C. McGee, Wilmington, Del. The nomination was seconded and it was moved that nominations be closed and that the Secretary cast a unanimous ballot for the election of Dr. McGee to the Committee on Credentials for a term of three years.

The motion was duly seconded and unanimously carried. The Secretary declared Dr. McGee duly elected.

CHAIRMAN PALMER: The next item of business is the election of members of the Advisory Committee on Postgraduate Courses. The Committee actually is appointive. There have been some changes in the personnel at one or two year intervals. It is customary to review the Committee and appoint perhaps one or two new members periodically.

DR. E. DICE LINEBERRY (Governor for ALABAMA): I move that the Chairman appoint the Committee for the coming year.

This motion was duly seconded and carried; and thereafter the Chairman reappointed Dr. Thomas M. McMillan, Chairman; Dr. Chester S. Keefer, Dr. Ralph A. Kinsella and Dr. Karver L. Puestow and appointed as a new member, succeeding Dr. José J. Centurión, of Cuba, Dr. Howard P. Lewis, of Portland, Ore.

CHAIRMAN PALMER: The next item on the agenda consists of two referred matters from the Board of Regents: (1) To ask Dr. LeRoy H. Sloan to present his suggestions of Governors' Committees of from 5 to 7 members in large cities to help evaluate or furnish information about candidates for membership.

DR. LEROY H. SLOAN: Mr. Chairman, in the deliberations of the Committee on Credentials, a great deal of information is needed before a candidate can be suitably passed upon. It is often extremely difficult for the Governor always to have an acquaintanceship with or to know anything about some particular candidate, and the Committee believes that the Governor could facilitate the handling of candidates if he would appoint an Advisory Committee to work with him. Some of the Committee feel that the personnel of the Governor's Committee should not be publicized and that it probably should be known to the Governor and the Executive Offices only; and that the responsibilities of the Committee would be to assist the Governor in collecting the necessary details concerning the character, ability and standing of candidates from that state or territory.

For example, in Chicago, there is a small Governor's Committee which has a wide acquaintanceship with the younger internists as well as the older ones; and this Committee sits down with the Governor and reviews all candidates before they are endorsed by the Governor. In Eastern New York, the Governor has a similar Committee for the area of Brooklyn and environs. Through such a Committee, the Governor may be able to obtain more accurate and comprehensive information about candidates and the candidate likewise is benefited by being given every opportunity to qualify.

CHAIRMAN PALMER: Thank you, Dr. Sloan. It was at Dr. Sloan's suggestion that I appointed such a Committee in Chicago, and it has been of very great help to me. I understand Dr. Lincoln has a similar Committee for Brooklyn and we should like to hear from him.

DR. ASA L. LINCOLN (Governor for Eastern NEW YORK): We have such a Committee working in Brooklyn, where many of our candidates originate. That Committee consists of a small group of internists from the Brooklyn Society of Internal Medicine. They meet, perhaps not as frequently as they should, about once

in two months when they require the proposer and seconder of the candidate to be present and they go over each candidate in full detail with the sponsors present. Recommendations from the Committee to me, as Governor, have been not only helpful but very good.

DR. GEORGE H. LATHROPE (Governor for NEW JERSEY): Mr. Chairman, there is a somewhat smaller community in which I live. Essex County, in New Jersey, is a rather densely populated area with probably over a million inhabitants. I have adopted the plan, which has been very satisfactory, to pick out each Autumn a group of men who are connected with the candidate's hospital or reside in his area and who, therefore, are able to give me first hand information. Generally it has been easier to find five or six such Fellows, who will act temporarily as the Governor's Committee. I find this plan a little more satisfactory than having just a single committee.

DR. HOWARD P. LEWIS (Governor for OREGON): This idea is fine for the larger cities but it need not be mandatory in a smaller community. I know every single man who is likely to come up for candidacy in the College and I can find out all about him.

CHAIRMAN PALMER: Dr. Sloan's remarks were in the way of suggestions; he did not intend any mandatory action be taken.

DR. JOSEPH D. MCCARTHY (Governor for NEBRASKA): I believe there are some of our routines that could be very greatly implemented and the Governors saved from certain embarrassing situations. I think proposal blanks should be distributed through the Governors only. Frequently the first the Governor knows about the candidacy of some individual is when he receives the proposal for endorsement. If it is desirable to have a screening process, we should consider some changes in our system. The Governor should know of a prospective candidate before any proposal is initiated and that can be accomplished by having all proposal forms distributed by the Governor and not by the Executive Offices of the College.

DR. J. MURRAY KINSMAN (Governor for KENTUCKY): So far as I know there has never been any proposal from Kentucky that has not passed through my hands.

SECRETARY LOVELAND: I think that Dr. McCarthy is referring to the fact that any Fellow in his State may write to my office for a proposal blank, saying he has a candidate to present. Instead of his getting the proposal form through the Governor, he writes to me. We have operated under the assumption that any Fellow of the College has the right to ask for a proposal form in order that he may present a candidate for membership. The proposal form eventually must pass through the Governor's office for endorsement before it may ever reach the Credentials Committee. We do not furnish proposal blanks direct to candidates for Associateship but we have given them out freely to Fellows who wish to propose candidates. In fact, there have been many instances where Governors have asked my office to send a proposal form directly to a candidate, and other cases in which the Governor has even told a prospective candidate to write to me for a proposal blank. The question presented is whether the several Governors wish to take on the added duty of distributing proposal blanks in their territories rather than having the College follow its old system. Our office is prepared and willing to follow the wishes of any particular Governor.

DR. DWIGHT L. WILBUR (Governor for Northern CALIFORNIA): I am in agreement with Dr. McCarthy's remarks. I move that this matter be taken up by the Board of Regents, namely, that all proposal blanks be put through the Governor for the State so that he will know ahead of time who is going to be proposed.

The motion was seconded by Dr. McCarthy and opened for discussion.

SECRETARY LOVELAND: I do not believe that this need be referred to the Board of Regents under present regulations of the Constitution and By-Laws. If the Governors desire to handle the proposals in this manner there could not be any objection to putting the proposal directly to vote in this Board.

CHAIRMAN PALMER: Mr. President, we should like to hear from you and President-Elect Middleton as to your views on this subject.

PRESIDENT FITZ: I do not see why it should go to the Board of Regents.

PRESIDENT-ELECT MIDDLETON: It should not go to the Board of Regents.

A GOVERNOR: The proposed new method would not affect me in a small state, but it seems to me that the plan would present considerable difficulty for a Governor in a large, thickly populated area. Some Governors will be in for a great deal of work and correspondence. I wish to offer the suggestion that this proposal be not mandatory but left to the Governor's personal discretion for his area.

DR. ROBERT WILSON, JR. (Governor for SOUTH CAROLINA): Under certain conditions, according to the By-Laws, a proposal may be endorsed by an Officer or Regent of the College and not necessarily by a Governor. I wonder whether this resolution might conflict with the By-Laws.

SECRETARY LOVELAND: It is true that under certain conditions, the By-Laws provide that a candidate may be endorsed by the Governor of his district or by an Officer or by a Regent. For a long time, however, the Board of Regents has been on record that it shall not be the policy of an Officer or Regent to endorse candidates, or for that matter, ever to propose or second a candidate. The only exception might be in the case of a candidate from some Central American country, where we have no Governor. Were he proposed for membership and were he personally known to an Officer or Regent and not personally known to any Governor, he could be endorsed by an Officer or Regent and still not transgress provisions of the By-Laws. Speaking further about the resolution, the proposal is simple enough in Nebraska, but it would place a tremendous burden upon the Governor for Eastern Pennsylvania or for Eastern New York or for many other densely populated areas. Already some of the Governors carry on a voluminous correspondence on behalf of the College. You may have no idea how many letters and telephone calls might be involved. My office, without other than the expressed wish of a Governor, will be glad to handle proposal forms as desired in any particular area.

DR. LINCOLN: The proposal would seem to be a good idea, but it occurs to me that the same purpose might be accomplished if the Executive Offices would notify the Governor of the names of candidates who are in the process of being proposed by Fellows from any particular area. That would give the Governor an opportunity to get advance information before the proposal form arrived in his office, and it would obviate the necessity of a large amount of correspondence.

DR. EDWARD C. REIFENSTEIN, SR. (Governor for Western NEW YORK): I wish to second what Mr. Loveland suggested as far as Western New York is concerned, for it would mean that I would have to have an extra secretary to care for the work. I know pretty well, under our present plan, what proposals are going through. I would like to have the present plan continued and to have Mr. Loveland's office distribute the proposal forms to Fellows; then I would favor Dr. Lincoln's suggestion that Mr. Loveland's office inform me of the names of prospective candidates and the names of Fellows who expect to sponsor them. If I think the candidate is not yet ready, I shall have means of discouraging further progress on the proposal at once.

CHAIRMAN PALMER: Dr. Wilbur, I wonder if we could compromise these difficulties by re-stating your motion, to omit the recommendations to the Board of Regents and simply recommend to the Executive Secretary that he follow the wishes of the Governors in the respective territories.

DR. DWIGHT L. WILBUR (Governor for Northern CALIFORNIA): That will meet with my approval.

DR. JOSEPH D. MCCARTHY (Governor for NEBRASKA): It also meets with my approval.

Chairman Palmer submitted the motion to vote. There was a chorus of "ayes" and the motion was carried.

CHAIRMAN PALMER: Dr. Sloan, you did not include in your discussion the matter briefly discussed at the Combined Meeting of the Governors and Regents on April 16, and then referred to this Board, with respect to the work of the Conference Committee on Graduate Training in Medicine.

DR. LEROY H. SLOAN (Regent): I purposely omitted that subject because it seemed entirely a different field for discussion and I did not want to combine the two. I should like to hear some expressions from the Governors concerning the suggested program, and then to discuss it.

CHAIRMAN PALMER: We would like to know what the Governors think of the suggestion that they be requested from time to time to make recommendations to the Conference Committee with respect to personnel and teaching programs of certain hospitals within their area.

DR. J. O. RITCHEY (Governor for INDIANA): As I understand it, if the Governor himself should not wish to assume that responsibility he could call upon someone else in the general area of the hospital to take care of the matter. Is that correct?

DR. SLOAN: Yes.

PRESIDENT-ELECT MIDDLETON: I believe the ground was adequately covered in our Combined Meeting. There are certain angles, however, that may not be clear to all. In the first place, the task is not an overwhelming one. There will be scarcely more than 10 per cent of the hospitals in any event, and of those 10 per cent, it would not be our prediction that more than 1 per cent would require survey by a given Governor or his representative. Further, there is no desire on the part of the Conference Committee to put a Governor "on the spot." If the local situation is such that he cannot handle it, obviously he can delegate his authority or he may definitely request the Conference Committee to take the responsibility.

If I may reflect for a moment on the other aspect of the situation, the surveys in the past have been in the hands of the Council on Medical Education and Hospitals of the American Medical Association through which an expensive mechanism has been set up, one that should not be glibly duplicated by the numerous specialties. If the College were to support a central agency in Internal Medicine, it would be not only a loss of strength to the Council but an invasion by innumerable groups of specialties making surveys of every hospital in the land. Hospital administrators may already feel that these inspections may become a plague.

I believe that the Governors can lend a great deal of strength to the educational movement of the College, first, by participation, and, secondly, by avoiding duplication.

The fact that the Governors have been asked to take this responsibility brings to them a certain, definite function in behalf of the graduate education program of the country and if this is to be made realistic it must be directed toward the efficiency of the training within the individual hospital. Only the men on the scene can probably give an accurate account.

DR. LEROY H. SLOAN (Regent): The Conference Committee was formed before the War; it is now a reactivated Committee. After the War was over there was a great list of hospitals applying for approval of their residency training facilities. It became a problem to know what to do. There were two procedures possible—one, to allow the American Medical Association to rubber stamp those applications for approval; the other, to have a mechanism which would make it possible to consider individually these hopsitals. This is the mechanism your Committee has recommended.

Since the Committee has been at work, the Council has become much more hospital and educational minded. They are giving more detailed attention to this problem. The whole attitude has changed and changed decidedly for the better. We do not want that attitude to revert to its original state. We want the Council to know that the American College of Physicians and others in the field of Internal Medicine are standing by, taking a keen interest in this business and willing also to help evaluate

properly the hospitals. I think you will find hospitals on the approved list that ought to be taken off. You will have the privilege of writing to the Committee and giving it advice. There will be hospitals in your territory that you yourself know should be accredited fully; although the Conference Committee and the Council may not have sufficient information for a decision. In the large teaching centers, there is relatively little problem. But outside of these centers, and oftentimes nearby, there may be a hospital with an active teaching organization seeking accreditation. This hospital will submit its reports, the Conference Committee must look them over and determine whether those who are trying to teach are adequately qualified. Then the Committee must determine whether the program is actually going ahead, and that is where the Committee wants information from the Governors.

Once more may I say we do not want the attitude of the Council to change. The present forward-looking plan has been brought about by constant conferences with those in charge. It is highly important that your son and mine, when they finish medical school, shall know where to go to get their additional training, so that they may be assured that their training may be good and so that they may also be assured that they will be able to apply to the College or to other organizations.

CHAIRMAN PALMER: This requires no action. We shall pass to the next item, which has to do with a proposal made last year, to establish an indoctrination lecture for new members of the Board of Governors, in regard to their new duties and their responsibilities. New Governors are not elected until Thursday afternoon of the Annual Session and that creates a little difficulty in determining when this indoctrination lecture may be arranged. Might we try to arrange a meeting of the new Governors sometime Thursday afternoon or Friday morning or should they all be invited to come to the Philadelphia Headquarters to meet with the Committee on Credentials? Mr. Loveland, have you any thoughts on this matter?

SECRETARY LOVELAND: One of the best methods of teaching is the clinical method. If the new Governors could meet with the Credentials Committee at one of their stated meetings, at which they are working on candidates and discussing the multiple problems of qualifications, that would be the most effective way of giving them an adequate indoctrination. As a matter of fact, the Committee, on occasion in the past, has invited some particular Governor to meet with the Committee to discuss the problems in connection with candidates from that Governor's territory. The difficulty is that the Committee will not meet until November and there is an intervening period during which the new Governor will function without benefit of indoctrination. I may add that on the election of a new Governor we send him a fairly detailed outline of his duties but obviously we cannot adequately discuss the whole set of criteria for membership.

DR. GEORGE H. LATHROPE (Governor for NEW JERSEY): If there is relatively a small number of new Governors, I should suppose that the Credentials Committee would be extremely glad to have them attend a meeting. If the new Governors numbered more than six or seven, such a plan might clog up the Credentials Committee.

I think the retiring Governor should be responsible for this job of helping his successor and giving him all the information he can and to consult with him during the first year. This to me is sensible. To have the new Governors meet here on Thursday or Friday may be a good thing, but I believe the retiring Governor is the man who has to be responsible for helping him.

DR. J. MURRAY KINSMAN (Governor for KENTUCKY): Is it not known ahead of time who is going to be Governor?

SECRETARY LOVELAND: It is not necessarily known in my office. It might be possible to determine this in a measure through the Nominating Committee but the Nominating Committee does not have final decision. Any Fellow can nominate a Governor at the Business Meeting.

DR. KINSMAN: Would it not be feasible to announce at the end of the Business Meeting that the new Governors shall meet immediately or at the end of the Scientific Session? If that be not feasible, then I believe the new Governors should meet with the Credentials Committee.

DR. LEROY H. SLOAN (Regent): I do not think the expenditure of all that cost is justified.

DR. JOHN MINOR (Governor for the DISTRICT OF COLUMBIA): I think the problem is simple. Most of the Governors have at least a fair idea of what they are supposed to do. It seems to me that if we prepared a simple statement or pamphlet for the instruction of the new Governors, it would solve the whole problem satisfactorily. As it has been pointed out, if you have to bring a new Governor from California, Arizona or some other remote place to Philadelphia neither the expense nor the time can be justified.

DR. ROBERT WILSON, JR. (Governor for SOUTH CAROLINA): When first I became a Governor, I did not learn fully my duties until I had a year's experience and some time on the Credentials Committee. I think that that is really the most involved and educational feature in which newly elected Governors might participate. I agree that if there were a large number, the plan might not be effective and it might interfere with the work of the Credentials Committee. Sometimes the Committee has a tremendous amount of work to do in a stated time, and in that case taking extra time for explanations and discussions would not be so good.

A good many of the Governors could, and certainly at much less expense to the College, participate to some extent in the work of the Credentials Committee if the most recently elected ones could sit in at the Credentials Committee meeting which is held the day before the Annual Session begins. That would be a good time, coming at the end of the first year of the Governorship, after they know something about the problems. When a man does not know what the problems are, he does not know what questions to ask; whereas if he has held office for a year he is acquainted with the problems and such a meeting would be much more valuable to him. My suggestion, therefore, is that newly elected Governors, after one year, be invited to meet with the Credentials Committee at the time of the Annual Session.

DR. E. DICE LINEBERRY (Governor for ALABAMA): I came in as a Governor during the War, succeeding a man who was ill and unable to give me instructions. I do not believe we shall have a big turnover in the Governors in the future. I think that one of the previous hardships of the new Governors goes back to the time when the College was in the process of extending its membership. I do not believe that the problem is going to be as great for the new Governors as some think and I know our Executive Secretary will help all of the Governors, as he has helped me.

DR. DAVID W. CARTER, JR. (Governor for TEXAS): I should like to suggest that a manual be prepared for the guidance of new Governors. I am serving my first term and I know very little about the duties of the Governors except for letters sent me by the Chairman and the Executive Secretary. I believe that Mr. Loveland's office can very readily prepare a brief manual for the guidance of the new Governors and also that it would be of help to older Governors who may forget some of the things the College wants done.

PRESIDENT FITZ: I am deeply interested in this discussion. I feel that the Governors are so terribly important that personally I should like to support the idea of Dr. Kinsman that, if possible, we should have a meeting immediately after the election of Governors and not only have the Chairman of the Board present but also have the President of the College and Chairman of the Credentials Committee. The Governors are in an important position fundamentally in this College and they have the responsibility for the kind of members admitted to the College. I also think the idea of a pamphlet is fine, but I feel that it would be more important by far to have the President, the Chairman of the Board of Governors and the Chairman of the

Credentials Committee to talk to the new Governors, who would take their jobs more seriously and on the whole develop a greater interest.

CHAIRMAN PALMER: For the sake of formulating your thoughts, so that you may accept or turn down a proposal, would not it be a good idea for the Chair to entertain a motion to the effect that newly elected Governors be requested to meet in this room at 5:00 p.m. Thursday with the Chairman of the Board of Governors, the Chairman of the Credentials Committee, the President of the College and the Executive Secretary of the College in attendance.

DR. WILLIAM C. MENNINGER (Governor for KANSAS): There are a number of us who have become Governors in the past year. Do you include those also?

CHAIRMAN PALMER: I meant the ones to be elected on Thursday, but I am perfectly willing to increase the number to include any other Governors so interested.

DR. DWIGHT L. WILBUR (Governor for Northern CALIFORNIA): I should like to add a further amendment, first, that a brief manual be prepared for the guidance of the Governors, and, second, that the newly elected Governors be invited to attend the Credentials Committee meeting at the beginning of the Annual Session.

With the above amendments a motion was made, seconded and unanimously adopted, providing that newly elected Governors and other Governors so interested are to meet with the President, Chairman of the Board of Governors, Chairman of the Committee on Credentials and the Executive Secretary at 5:00 o'clock, Thursday, April 20; that the Executive Secretary be requested to prepare a manual for the instruction of Governors as a whole; and that the newly elected Governors be invited to attend the meeting of the Credentials Committee preceding the next Annual Session.

CHAIRMAN PALMER: Next on the agenda is the election of a Chairman of the Board of Governors for a period of three years, until 1953.

DR. HARRY T. FRENCH (Governor for NEW HAMPSHIRE): I nominate Dr. Walter L. Palmer for reëlection, as Chairman of the Board of Governors.

DR. PAUL F. WHITAKER (Governor for NORTH CAROLINA): I second the motion and move that the nominations be closed and that the Secretary cast one ballot for the election of Dr. Palmer.

Chairman Palmer put the motion to vote and it was unanimously adopted. (Applause.)

CHAIRMAN PALMER: Thank you very much, gentlemen. The meeting is now open for discussion of regional meetings and regional activities. Dr. Fitz spoke the other day in appreciation of regional meetings. Do you have further comment, Dr. Fitz?

PRESIDENT FITZ: My only fault with the Governors is that I do not think they are half enough conceited. The work of the Governors is of tremendous importance. I think the regional meetings that I attended were the highest type of medical meeting with reference to Internal Medicine. The Governors do a fine job at organizing the programs and the sessions are carried through effectively. The audiences attracted by such meetings and the value of these meetings are not recognized as they ought to be. I merely want to say that any Governor who has anything to do with this kind of a meeting does a most significant piece of work for the College and I hope that the regional meetings will continue on the same plane as in the past few years.

DR. LEMUEL C. MCGEE (Governor for DELAWARE): I move that the College express its thanks to President Fitz and his officers and to our Regents for their personal interest in the regional meetings and their attendance and participation throughout the past year.

The motion was duly seconded by Dr. Reifenstein and others and unanimously carried.

CHAIRMAN PALMER: I want to add my personal word of appreciation too. Dr. Fitz and Dr. Middleton and others have devoted a great deal of time and effort to these meetings and their presence has been most valuable and important.

DR. EDWARD L. BORTZ (Regent): Mr. Chairman, those of the Governors who have followed the development of the regional meetings over the past ten years know how tremendously important they are in the areas where they have been held. We get a great lift out of the regional meetings in Eastern Pennsylvania. It so happens that there are other cities and communities that would also like to have the regional meetings held in their midst and I should like to recommend for the consideration of each Governor that wherever it is possible a certain rotation in the place of holding the meeting will result in a further invaluable service to the Fellows and Associates in that area. You will also be giving a lift to the profession in general by doing so.

We have found that not only the members of the College but younger men coming along, who are good College material, find great inspiration in attending these meetings. For instance, in Eastern Pennsylvania, instead of holding the Regional Meeting every year in Philadelphia, if the loyalty of our membership would support it, I think we should hold a meeting occasionally in Harrisburg, Wilkes-Barre, Scranton or some other city. This would bring the forceful support of the College to a higher level of practice not only among internists but among the general practitioners of medicine and there would be a stimulus to the profession in general.

CHAIRMAN PALMER: In line with the comments which Dr. Bortz has made, it may interest you to know the experience of the Midwest. It has been exactly as he has outlined it to you. Dr. Donald, our Governor for Michigan, and Dr. Ritchey, our Governor for Indiana, commented only yesterday to the effect that when we moved the Regional Meeting out of Chicago and went to Milwaukee and Detroit and Indianapolis, the attendance at each meeting came about half from the local area and about half from outside, and the stimulating effect of the Regional Meetings in those localities was very great.

DR. RAFAEL RODRIGUEZ-MOLINA (Governor for PUERTO RICO): Last year we were able to conduct our first Regional Meeting in Puerto Rico. We feel very grateful to you and to the members of the College for having sent Dr. Hugh Morgan to us for this meeting. I have had several requests already from physicians outside of the College in Puerto Rico for another meeting of this character down our way.

DR. PAUL F. WHITAKER (Governor for NORTH CAROLINA): Mr. Chairman, for those of us who hold our regional meetings in more or less isolated areas, we want to include Mr. Loveland on the list of those who are most helpful and I should like to have the Board express our personal thanks for the very efficient services rendered by our Executive Secretary in getting the meetings under way, having the programs printed, etc., for he is always in there pitching.

CHAIRMAN PALMER: Because of your enthusiastic approval, we shall certainly include Mr. Loveland in the list to whom the general expression of thanks was given.

SECRETARY LOVELAND: I trust you have all kept the outline of the regional meetings planned for the coming months. Many of you are planning regional meetings and you want to get them on the list. You will see that some of the Governors have planned far in advance and have already obtained acceptances from the President or other Officer or Regent of the College. Obviously these gentlemen cannot be in two or three places on the same week-end. To help us, try to get your meeting scheduled so that I may know long in advance and can help other Governors to avoid conflicts.

DR. E. DICE LINEBERRY (Governor for ALABAMA): I believe we should always inform the Secretary in planning our meetings.

DR. HOWARD P. LEWIS (Governor for OREGON): In the Northwest, we have something that we think is going to work out very well. We have set a date in November, the second Friday and Saturday each year, which will be recurrent so

that every member of the Northwest will know exactly when the Regional Meeting is going to be held and he can plan accordingly.

PRESIDENT FITZ: May I add another word? I have found this year that in planning the Annual Session, the regional meetings were a great help to me. For instance, I have a speaker on one of the General Sessions whom I first heard at a regional meeting in Alabama. It would be a fine thing if the Governor, who is responsible for a regional meeting, would take the trouble to send to the President a suggestion as to which paper on his program really seemed to him the best and the most popular. We hear such good papers from Fellows and Associates of the College at these meetings that it might be very helpful if some of these strikingly good papers could be reproduced on the General Sessions program.

CHAIRMAN PALMER: Does anybody have any other item they wish to present?

DR. GEORGE H. LATHROPE: I want to make a motion. In order to bring this subject definitely before the meeting, I move that the Board of Governors recommend to the Board of Regents of the College that proper steps be taken to establish 35 years as the minimum age for Associateship.

Dr. McGee (Governor for DELAWARE) seconded the motion and the matter was opened for discussion.

DR. LATHROPE: May I explain my motion a little bit. I think a resumé of what was said at the Sunday evening meeting might help and it might refresh your minds.

There appears to be a pretty general notion that the quantitative growth of the College has come to a point where it is interfering with the qualitative progress. I have not heard as yet any very practical suggestions for reducing the numbers. This proposal is not only for quantitative improvement, that is, reducing the numbers, but it also is for qualitative improvement, as I shall try to explain.

Let me repeat the figures which were made out from three different meetings of the Credentials Committee. There were 317 Associate candidates, of whom 124 were 35 years old or under. That constitutes 42 per cent. Of the candidates for Fellowship there were 105 that were 38 years of age or under. You can safely say that such a limitation in age would mean somewhere between 30 and 40 per cent difference in the number of applicants, for Associateship on the one hand and for advancement to Fellowship on the other hand, the very first year.

Now, as to one or two of the other advantages, from a qualitative standpoint, the thing that impresses me is that when the College gives a man a Fellowship he should be a mature, well-seasoned internist. Our public relations are very important and that is what we really certify to the public when we make a man a Fellow of the College of Physicians. We are saying he is well-seasoned, that he has had experience, that he is mature, that he is a man to whom they can take their problems.

Another point is this, the addition of six years or so to the period in which a man has to attempt qualifying for Fellowship brings about a better separation between the American Board of Internal Medicine, on the one hand, and Fellowship in the College, on the other hand. It makes Fellowship a much more dignified thing than it now is, when very often it comes right on top of a man's certification, and that is the reason for so many coming into the College now. If they pass the Boards, they expect to walk right into the College of Physicians. I do not think it is bad to keep a man working for two years longer. I have seen some of the men who attain certification and Fellowship in the College just sit down and do nothing thereafter. By the time a man is 40, if he becomes a Fellow and he has been working all of those years for it, it makes a bigger impression on him and that extra period has inculcated habits of study.

(Vice-Chairman Charles A. Doan assumed the Chair).

VICE-CHAIRMAN DOAN: Is there further comment or discussion?

DR. JOSEPH D. MCCARTHY (Governor for NEBRASKA): Mr. Chairman, I am wondering if the requirements for Associateship, calling for three years' residence

in a community, do not almost automatically raise the age of candidates to 35. By the time a man is through with his training, internship and residency, and becomes established in a permanent location for three years, he will be almost 35.

DR. LATHROPE: There was a candidate on my list who was only 29 and there were four or five out of the whole group of candidates who were not more than 31.

DR. E. DICE LINEBERRY (Governor for ALABAMA): If we wish to add a time limit, I think it should be in mental years and not just time. Therefore, I object to an age limit. If we should add years to the period of practice, that might be a different matter but I do not believe we should limit it by age.

VICE-CHAIRMAN DOAN: I call your attention to comments made by Dr. David Barr, a few nights ago, in which he suggested that rather than place an age limit for Associateship it might be feasible to extend the time for Fellowship. I should like to hear some discussion about that aspect of controlling the situation, so that the younger candidates will continue to work because Fellowship will be the real goal.

DR. HARRY T. FRENCH (Governor for NEW HAMPSHIRE): It seems that one of the functions of the College is the development of these young men after they have passed their graduate days, and if they have the opportunity to become Associates it gives them a chance to attend our postgraduate courses and an added stimulus to keep on with their training. Furthermore, many of these young men, after they finish their residencies, are lost to a certain extent as to further training. Associateship provides this opportunity and I should be much more in favor of extending the length of Associateship than of limiting the age at which a candidate may be elected.

DR. KARVER L. PUESTOW (Governor for WISCONSIN): I am not in favor of an age limit.

DR. DWIGHT L. WILBUR (Governor for Northern CALIFORNIA): I think it would be a bad mistake for the College to make itself an old man's club. There are many very capable and able young internists between the ages of 30 and 35 and for us to say that a man must be 35 before he is admitted to Associateship would be a bad mistake indeed. I recognize that there are serious difficulties which the College faces in the matter of controlling its size. The problem cannot be answered at this meeting. Might it not be reasonable to suggest that a committee be proposed to study this matter and to report back to the Board of Governors at its meeting next year?

DR. ELLSWORTH L. AMIDON (Governor for VERMONT): I am a little confused about Dr. Barr's suggestion. I do not understand how that would cut down the membership, especially the attendance at our Annual Sessions, and that is one of our chief problems. Furthermore, no one has discussed the very fine effect that this period of five years has on the encouragement and stimulation of Associates. I favor the five year period.

VICE-CHAIRMAN DOAN: The question is, in connection with Dr. Lathrope's motion, of limiting the age to a minimum of 35 years for eligibility to Associateship in the College with recommendation from the Board of Governors to the Board of Regents for adoption. All those who are in favor of this motion will please signify by saying "aye"; those opposed, "no."

There was an overwhelming "no" vote and the motion was lost.

DR. THOMAS P. MURDOCK (Governor for CONNECTICUT): Mr. Chairman, I now move the adoption of the suggestion of Dr. Wilbur, that a Committee be established to survey the whole situation and to bring back a report and recommendations at the next meeting of this Board.*

The motion was duly seconded by several and unanimously carried.

(Chairman Palmer then resumed the Chair).

DR. ROBERT WILSON, JR. (Governor for SOUTH CAROLINA): Last year in New York there were many complaints about the inability of members to get seats in the

* Thereafter, Chairman Palmer appointed the Governors' Survey Committee: Charles A. Doan, Chairman, Dwight L. Wilbur, Robert Wilson, Jr.

various meetings. This year, at Boston, I have heard a good many comments on how the situation has improved. All are able to get in to the meetings and the meetings are not nearly so crowded. That may be simply because New York's facilities were smaller than those at Boston. Then again it may be because of the success of the plan adopted last year to restrict the number of guests. We proposed the new plan be tried for a year. I think the plan of limitation of guest attendance is probably the most responsible factor in this improved situation and I should like to move that it is the sense of this group that the present plan be continued. The motion was duly seconded and opened for discussion.

DR. DOUGLAS DONALD (Governor for MICHIGAN): I should like to ask if the raising of the registration fee to $25.00 has cut down the attendance appreciably.

SECRETARY LOVELAND: We have had very few complaints from members but no end of complaints from non-members, who object to the $25.00 assessment and also object to being excluded unless the fee is paid. I have not had an opportunity to analyze the number of non-members who have registered in comparison with the number of non-members last year but I have the definite impression that the new plan has not been as effective as hoped for. I think the plan well worth continuing and I believe we can improve it further next year.

The Chairman put the motion to a vote and it was carried.

CHAIRMAN PALMER: Are there other matters to be considered?

DR. HAROLD W. GREGG (Governor for MONTANA and WYOMING): From the hinterlands, I have heard a good deal about the postgraduate courses and noted that none of them is conducted just before or just after the Annual Session. I do not know the mechanics of their operation but I am wondering if there is a possibility of scheduling some courses just before or just after the Annual Session, as we used to do.

CHAIRMAN PALMER: The Chair suggests that this question be referred to the Advisory Committee on Postgraduate Courses.

At the meeting of the Board of Regents yesterday a resolution, which I shall read, was adopted, and it will be presented to the membership at large for adoption at the Annual Business Meeting tomorrow.

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The term of some members of this Board will expire at this meeting. May I ask the Governors whose terms expire now and who are not eligible for reëlection to stand.

(Seven men stood).

CHAIRMAN PALMER: Now I shall ask you to sit down and now ask the rest of the members to rise in a vote of appreciation for the splendid years of service these men have given.

(The members rose and there was prolonged applause.)

Adjournment.

Attest: E. R. LOVELAND,
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Course No. 1, INTERNAL MEDICINE: SELECTED SUBJECTS. University of Pittsburgh School of Medicine, Pittsburgh, Pa.; R. R. Snowden, M.D., F.A.C.P., Director; one week, September 25–30. Fees: A.C.P. Members, $30.00; Non-members, $60.00.

Course No. 2, PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE. Duke University School of Medicine, Durham, N. C.; Eugene A. Stead, Jr., M.D., F.A.C.P., Director; one week, October 9–14. Fees: A.C.P. Members, $30.00; Non-members, $60.00.

Course No. 3, CRITICAL PROBLEMS IN INTERNAL MEDICINE. University of Chicago School of Medicine, Chicago, Ill.; Wright Adams, M.D., F.A.C.P., Director; one week, October 23–27. Fees: A.C.P. Members, $30.00; Non-members, $60.00.

Course No. 4, CLINICAL ALLERGY. Roosevelt Hospital Institute of Allergy, New York, N. Y.; Robert A. Cooke, M.D., F.A.C.P., Director; two weeks, October 23–November 3. Fees: A.C.P. Members, $120.00; Non-members, $240.00.

Course No. 5, RECENT DEVELOPMENTS IN MEDICINE. University of Utah College of Medicine, Salt Lake City, Utah; Max M. Wintrobe, M.D., F.A.C.P., Director; one week, November 6–11. Fees: A.C.P. Members, $30.00; Non-members, $60.00.

Course No. 6, PERIPHERAL VASCULAR DISEASES INCLUDING HYPERTENSION. Mayo Clinic and Mayo Foundation, Rochester, Minn.; Walter F. Kvale, M.D., F.A.C.P., Director; and Edgar V. Allen, M.D., F.A.C.P., Nelson W. Barker, M.D., F.A.C.P., John E. Estes, M.D., Edgar A. Hines, Jr., M.D., F.A.C.P., and Richard M. Shick, M.D., F.A.C.P., Co-Directors; one week, November 27–December 2. Fees: A.C.P. Members, $30.00; Non-members, $60.00.

Course No. 7, GASTRO-ENTEROLOGY. University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director; one week, December 4–9. Fees: A.C.P. Members, $30.00; Non-members, $60.00.

Course No. 8, SELECTED ASPECTS OF CLINICAL HEMATOLOGY. New England Medical Center, Boston, Mass.; William Dameshek, M.D., F.A.C.P., Director; one week, December 11–16. Fees: A.C.P. Members, $30.00; Non-members, $60.00.

Course No. 9, MODERN TRENDS IN THE DIAGNOSIS AND TREATMENT OF HEART DISEASE. Woman's Medical College of Pennsylvania and other Philadelphia institutions, Philadelphia, Pa.; William G. Leaman, Jr., M.D., F.A.C.P., Director; one week, January 22–27, 1951. Fees: A.C.P. Members, $30.00; Non-members, $60.00.

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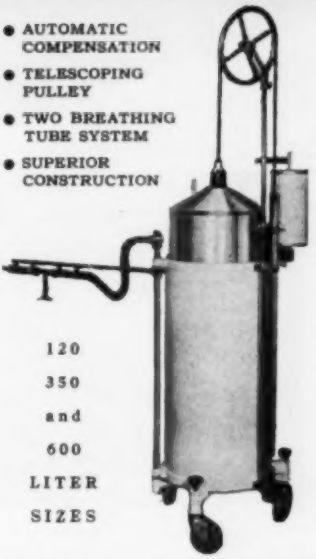

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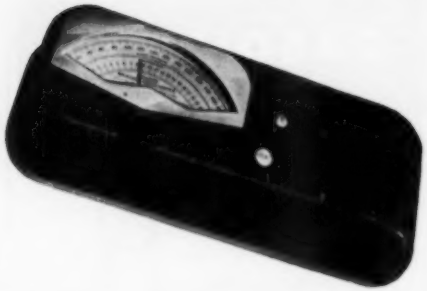

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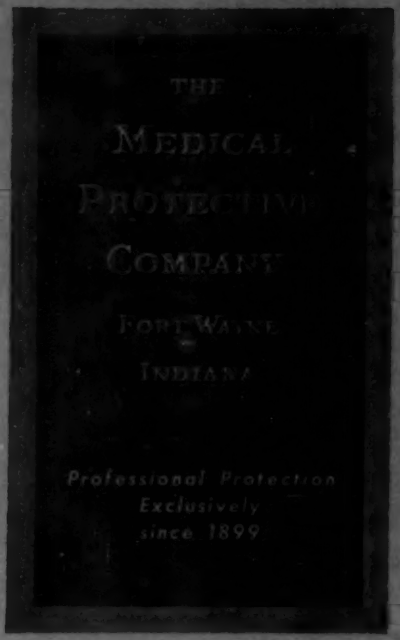

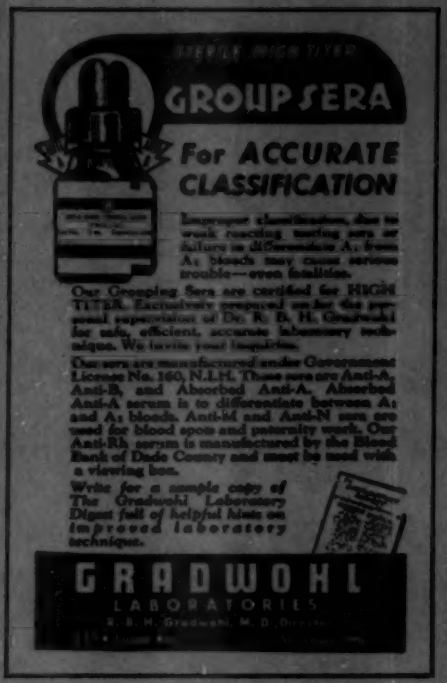
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